Dermatology
beyond the skin

Cover Page

Official title: A Randomised, Double-blind, Placebo-controlled, Parallel-group, Multi-centre, Phase 3 Trial Investigating the Efficacy, Safety, and Tolerability of Tralokinumab Administered in Combination With Topical Corticosteroids to Adult Subjects With Severe Atopic Dermatitis Who Are Not Adequately Controlled With or Have Contraindications to Oral Cyclosporine A
LEO Pharma number: LP0162-1346
NCT number: NCT03761537
Date: 15-Jun-2020

Updated Clinical Trial Protocol

LP0162-1346

Tralokinumab in combination with topical corticosteroids in subjects with severe atopic dermatitis who are not adequately controlled with or have contraindications to oral cyclosporine A
ECZTRA 7 (ECZema TRAlokinumab trial no. 7)

Phase 3 – efficacy and safety trial

A randomised, double-blind, placebo-controlled, parallel-group, multi-centre, phase 3 trial investigating the efficacy, safety, and tolerability of tralokinumab administered in combination with topical corticosteroids to adult subjects with severe atopic dermatitis who are not adequately controlled with or have contraindications to oral cyclosporine A

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:**	**LP0162-1346**
	Date:	**15-Jun-2020**
	EudraCT no:	**2018-000747-76**
	Version:	**4.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S (hereafter: 'LEO')

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

PPD, MSc Stat
Biostatistics Lead, Medical Sciences

PPD, MD, PhD
Medical Lead, Medical Sciences

PPD, RN, PhD
Clinical Operations Lead, Global Clinical Operations

PPD, MD
Vice President, Medical Sciences

Approval statement signatory investigator

The signatory investigator approves the clinical trial protocol and consolidated clinical trial protocol(s) comprising any subsequent amendment(s) by manually signing the Signatory Investigator Clinical Trial Protocol Approval Form, which is a separate document appended to this document.

The following person has approved this clinical trial protocol:

PPD, Prof. Dr. med
Signatory investigator

Acknowledgement statement investigator

Each participating investigator must agree to the approved clinical trial protocol by signing a Clinical Trial Protocol Acknowledgement Form or similar document.

Protocol amendment summary of changes table

Document history

Document	Date	Type of protocol amendment
Amendment 3 (substantial)	15-Jun-2020	Global
Amendment 2 (non-substantial)	19-Aug-2019	Global
Amendment 1 (substantial)	13-Nov-2018	Global
Original protocol	20-Jun-2018	NA

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

Amendment 3 (15-Jun-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.

Overall rationale for the amendment

The main reason for the amendment is to modify the statistical analyses to account for the unusually high number of missing information due to the Coronavirus Disease 2019 (COVID-19) pandemic in this trial. Statistical analysis was therefore revisited to ensure an unbiased evaluation of the treatment effect in the trial.

The contingency measures to minimise the impact of the COVID-19 pandemic on this trial are already implemented by 2 addendums. The first addendum gives an opportunity for the subjects to continue treatment with tralokinumab via home-use (self-injection) to provide continued therapy and ensure the safety of the subjects (Appendix 8, COVID-19). The second addendum includes the possibility of remote assessments related to efficacy via a mobile application (Appendix 9, *Imagine for Studies*). The second addendum has been submitted to the Ethics Committees in Poland and Spain.

Note: The table below describes 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
Approval statement LEO Pharma A/S (hereafter: 'LEO')	Medical Sciences and Safety has been changed to Medical Sciences. Biostatistics is now part of Medical Sciences.	To reflect a restructuring and change of department names within LEO Pharma.
Synopsis	'Statistical methods' section is updated.	To align with the changes in the relevant sections.
6 Trial objectives and endpoints	Additional endpoints are added to the table. *Supporting primary endpoint* • **Percent change from baseline to Week 16 in EASI score** *Supporting secondary endpoints related to the severity and extent of AD* • **Percent change from baseline to Week 26 in EASI score** • **Percent change from baseline to Week 16 in SCORAD** • **Percent change from baseline to Week 26 in SCORAD** *Supporting the secondary endpoint related to itch* • **Percent change from baseline to Week 16 in Worst Daily Pruritus NRS (weekly average)** • **Percent change from baseline to Week 26 in Worst Daily Pruritus NRS (weekly average)** • **Percent change from baseline to Week 16 in Eczema-related Sleep NRS (weekly average)** • **Percent change from baseline to Week 26 in Eczema-related Sleep NRS (weekly average)** *Supporting the secondary endpoint related to health-related quality of life* • **Change from baseline to Week 16 in EQ-5D-5L VAS score** • **Change from baseline to Week 26 in EQ-5D-5L VAS score**	To better evaluate the treatment effect.

Section no. and name	Description of change	Brief rationale
	• **HADS-anxiety and HADS-depression scores < 8 at Week 16** • **HADS-anxiety and HADS-depression scores < 8 at Week 26** • **Change from baseline to Week 16 in HADS-anxiety score** • **Change from baseline to Week 26 in HADS-anxiety score** • **Change from baseline to Week 16 in HADS-depression score** • **Change from baseline to Week 26 in HADS-depression score**	
14.2 Trial analysis sets	All subjects randomised to treatment **and exposed to the IMP** will be included in the full analysis set (FAS) and will be analysed for efficacy.	To exclude subjects who do not have any causal relationship with the IMP (to be in line with ICH E9 guideline).
	2 safety analysis sets are defined, one for the treatment period and the other for the safety follow-up period.	To differentiate the periods of active and no IMP treatment.
	The decisions regarding inclusion/exclusion of subjects from the trial analysis sets will be documented in the ~~statistical analysis plan update~~ **analysis set definition document** before breaking the randomisation code.	To update with the internal LEO process.
14.3.1 Aspects related to the COVID-19 pandemic	New subsection added.	To elaborate on the COVID-19 pandemic-related aspects that require special considerations in the statistical analyses.
14.3.2 ~~14.3.1~~ Disposition of subjects	**Permanent discontinuation of IMP due to the COVID-19 pandemic will be added to the list of reasons and identified based on the information documented in the eCRF.**	To capture the COVID-19 pandemic-related information.
14.3.4 ~~14.3.3~~ Exposure and treatment compliance	Treatment compliance will be presented for **the total missed IMP doses, missed IMP doses not due to the COVID-19 pandemic, and the missed IMP doses due to the COVID-19 pandemic for** the safety analysis set for each treatment group.	To present the COVID-19 pandemic-related information.
14.3.5 Rescue treatment	New subsection added.	To clarify the definition of rescue treatment.

Section no. and name	Description of change	Brief rationale
14.3.6 ~~14.3.4~~ Testing strategy	**Hypothesis testing will be based on the primary analysis of the primary estimand for each associated endpoint.**	To add clarification.
14.3.7 Intercurrent events	New subsection added.	To add clarification on the intercurrent events.
	1 additional intercurrent event and 1 attribute have been included. • **Subject-onset of the COVID-19 pandemic** (subject-specific intercurrent event) • **Missing due to COVID-19** (data attribute)	To maintain the trial integrity with respect to the original research questions and ensure an unbiased evaluation of the treatment effect.
	Panel 13 has been added.	To give an overview of the handling of data in relation to intercurrent events in each estimand.
14.3.8 ~~14.3.5~~ Analysis of primary efficacy endpoint	~~Three~~ **4** estimands addressing different aspects of the trial objectives will be defined: • **Primary estimand: 'COVID-19 modified composite'** • **Secondary**~~Primary~~ estimand: 'composite' • **Tertiary**~~Secondary~~ estimand: 'treatment policy' • **Quaternary**~~Tertiary~~ estimand: 'hypothetical'	To maintain the trial integrity with respect to the original research questions and ensure an unbiased evaluation of the treatment effect.
14.3.8.1 Primary estimand: 'COVID-19 modified composite'	New subsection added.	To maintain the trial integrity with respect to the original research question and ensure an unbiased evaluation of the treatment effect.
14.3.8.2 ~~14.3.5.1~~ **Secondary** ~~Primary~~ estimand: 'composite'	Treatment difference in response rates of EASI75 after 16 weeks achieved without either rescue treatment or treatment discontinuation**, as if the COVID 19 pandemic did not happen**	To maintain the trial integrity with respect to the original research question and ensure an unbiased evaluation of the treatment effect.

Section no. and name	Description of change	Brief rationale
	Subjects who prior to the Week 16 visit have received rescue treatment **or permanently discontinued IMP** will be considered non-responders.	To reflect the new 'composite' estimand approach.
	Removal of stratification variable 'country (Germany: yes/no)' in the analysis.	Limited number of subjects in the strata with 'country (Germany: yes/no) = yes'.
	'Sensitivity analyses for the ~~primary~~ **secondary** estimand' has been re-written.	To reflect the changes in the handling of missing data.
14.3.8.3 ~~14.3.5.2~~ **Tertiary** ~~Secondary~~ estimand: 'treatment policy'	Treatment difference in response rate **of EASI75** after 16 weeks between tralokinumab+TCS and placebo+TCS regardless of rescue treatment and IMP discontinuation**, as if the COVID-19 pandemic did not happen** Data retrieved at Week 16 for subjects who **prior to Week 16** have permanently discontinued IMP ~~prior to Week 16~~ **for other reasons than the COVID-19 pandemic** will be included in the analysis. **For subjects who have subject-onset of the COVID-19 pandemic prior to Week 16 and prior to any permanent discontinuation of IMP not due to the COVID-19 pandemic, any observed data from these subjects will be ignored and treated as missing in the same manner as missing data from not discontinued subjects in the analysis.**	To maintain the trial integrity with respect to the original research question and ensure an unbiased evaluation of the treatment effect.
	Removal of stratification variable 'country (Germany: yes/no)' in the analyses.	Limited number of subjects in the strata with 'country (Germany: yes/no) = yes'.

Section no. and name	Description of change	Brief rationale
	'Sensitivity analyses for the ~~secondary~~ **tertiary** estimand' has been edited. **In case the number of discontinued subjects attending the nominal Week 16 visit is too low to fit the imputation model in the primary analysis of the tertiary estimand, the sensitivity analysis will become the primary analysis of the tertiary 'treatment policy' estimand.**	To reflect the changes in the handling of missing data in the sensitivity analysis.
14.3.8.4 ~~14.3.5.3~~ **Quaternary** ~~Tertiary~~ estimand: 'hypothetical'	Treatment difference in response rates of 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 made available ~~before Week 16~~, **and as if the COVID-19 pandemic did not happen before Week 16.** Data collected after permanent discontinuation of IMP ~~or~~**,** after initiation of rescue treatment, **or after subject-onset of the COVID-19 pandemic** will not be included in the analysis.	To maintain the trial integrity with respect to the original research question and ensure an unbiased evaluation of the treatment effect.
	Removal of stratification variable 'country (Germany: yes/no)' in the analyses.	Limited number of subjects in the strata with 'country (Germany: yes/no) = yes'.
	Rather than assuming that observations are MAR within each treatment group, it is assumed that missing data from subjects who ~~discontinue treatment/receive rescue treatment~~ **had any of the intercurrent events** in the tralokinumab+TCS group will resemble missing data from subjects from the placebo+TCS group who ~~do not discontinue treatment/receive rescue treatment~~ **had none of the intercurrent events**.	To reflect the changes in the handling of missing data.

Section no. and name	Description of change	Brief rationale
14.3.9 ~~14.3.6~~ Analysis of secondary endpoints	**Only subjects with an average Worst Daily Pruritus NRS score of 4 or above at baseline will be included in these analyses.**	To clarify the further specification of the analysis.
	For each of the binary secondary endpoints, tipping-point analyses using the method described for the tipping-point analyses of the binary primary endpoint (EASI75 at Week 16) will be added as sensitivity analyses for the primary estimand.	To align the secondary endpoints to the primary endpoint.
	Interaction between subgroups and treatment effect will be tested using the ~~Breslow-Day test.~~**conditional logistic regression.**	To assess consistency in the treatment effect across subgroups.
	Subgroup analysis of IGA has been added.	To assess consistency in the treatment effect across subgroups.
	3 estimands addressing different aspects of the trial objectives are defined: • **Primary estimand: 'hypothetical'** • **Secondary estimand: 'treatment policy'** • **Tertiary estimand: 'COVID-19 modified composite'**	To maintain the trial integrity with respect to the original research questions and ensure an unbiased evaluation of the treatment effect.
14.3.9.1 ~~14.3.6.1~~ Primary estimand for the continuous secondary endpoints: 'hypothetical'	Treatment difference in change from baseline to Week 16/ Week 26 in SCORAD and DLQI scores, respectively, if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently**,** ~~and~~ no rescue treatment was made available**, and as if the COVID-19 pandemic did not happen before Week 16/Week 26.**	To maintain the trial integrity with respect to the original research question and ensure an unbiased evaluation of the treatment effect.
	Data collected after permanent discontinuation of IMP ~~or~~**,** after initiation of rescue treatment, **or after subject-onset of the COVID-19 pandemic** will not be included in the analysis.	To maintain the trial integrity with respect to the original research question and ensure an unbiased evaluation of the treatment effect.

Section no. and name	Description of change	Brief rationale
	Rather than assuming that observations are MAR within each treatment group, it is assumed that missing data from subjects who ~~discontinue treatment/receive rescue treatment~~ **had any of the intercurrent events** in the tralokinumab+TCS group will resemble missing data from subjects from the placebo+TCS group who ~~do not discontinue treatment/receive rescue treatment~~ **had none of the intercurrent events**.	To reflect the changes in the handling of missing data in the sensitivity analysis.
14.3.9.2 ~~14.3.6.2~~ Secondary estimand for the continuous secondary endpoints: 'treatment policy'	Treatment difference in change from baseline to Week 16/ Week 26 in SCORAD and DLQI scores, respectively, between tralokinumab+TCS and placebo+TCS regardless of rescue treatment use and treatment discontinuation**, as if the COVID-19 pandemic did not happen.** Data retrieved at Week 16 / Week 26 for subjects who **prior to Week 16 /Week 26** have permanently discontinued IMP ~~prior to Week 16 / Week 26~~ **for other reasons than the COVID-19 pandemic** will be included in the analysis. **For subjects who have subject-onset of the COVID-19 pandemic prior to Week 16/ Week 26 and prior to any permanent discontinuation of IMP not due to the COVID-19 pandemic, any observed data from these subjects will be ignored and treated as missing in the same manner as missing data from not discontinued subjects in the analysis.**	To maintain the trial integrity with respect to the original research question and ensure an unbiased evaluation of the treatment effect.
	In that case, the preferred order of elimination of the effects from the imputation model will be: **country,** prior CSA use, ~~country,~~ baseline disease severity, and baseline SCORAD/DLQI.	To reflect the updated order of importance of the stratification variables.

Section no. and name	Description of change	Brief rationale
14.3.9.3 ~~14.3.6.3~~ **Tertiary estimand for the continuous secondary endpoints: 'COVID-19 modified composite'**	New subsection added.	To ensure an unbiased evaluation of the treatment effect despite unexpected increase in missing data caused by the COVID-19 pandemic.
14.3.9.4 Subgroup analysis of continuous endpoints	DLQI endpoints are added for subgroup analysis of continuous endpoints.	To be consistent in the efficacy assessment across different endpoints.
14.3.10 ~~14.3.7~~ Analysis of other endpoints	To evaluate the efficacy related to health care resource utilisation, the amount of TCS used (assessed as the amount of TCS used between visits) **will be determined over 2-week periods**, and the number of days without topical treatment use (collected as Patient Days of Topical Treatment Use in the eDiary) will be determined over ~~2~~ **1**-week periods.	To better characterise the treatment effect over time.
14.3.11 Analysis of exploratory supporting endpoints	New subsection added.	To evaluate the treatment effect over time.
14.3.13 ~~14.3.9~~ Analysis of safety	The analyses of safety will be based on the safety analysis set **and the safety follow-up analysis set**.	To align with the change in the trial analysis set definition.

Section no. and name	Description of change	Brief rationale
14.3.13.1 ~~14.3.9.1~~ Adverse events	**Due to the COVID-19 pandemic and the implementation of home-use (self-injection) with telephone/video follow-up, overall safety monitoring could be impacted. To assess this, all AEs collected prior to and after the start of the COVID-19 pandemic will, in addition to being presented together, be presented separately for the overall summary of AEs and all treatment-emergent AEs by SOC and PT.**	To report plausible COVID-19 pandemic related issues in the data.
14.3.12.1 ~~14.3.9.1~~ 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, **1st quartile, 3rd quartile**, minimum, and maximum values for the safety analysis set~~ and the continuation treatment safety analysis set~~.	To better characterise the summary data for vital signs. To correct a mistake in the text.
	Vital signs will be listed for the safety follow-up analysis set.	Due to high number of subjects proceeding to ECZTEND trial, it is not expected to have enough subjects to warrant a summary.
14.3.13.1 ~~14.3.9.1~~ Laboratory parameters	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, **1st quartile, 3rd quartile,** minimum, and maximum values for the safety analysis set ~~and the continuation treatment safety analysis set~~.	To better characterise the summary data for vital signs. To correct a mistake in the text.
	Laboratory parameters will be listed for the safety follow-up analysis set.	Due to high number of subjects proceeding to ECZTEND trial, it is not expected to have enough subjects to warrant a summary.

Section no. and name	Description of change	Brief rationale
14.3.13.4 ~~14.3.9.4~~ Anti-drug antibodies	Summary will include 1st and 3rd quartiles.	To better characterise the summary data for vital signs.
	ADA categorisation has been specified	To add more clarification of ADA categorisation.
	For subjects who develop ADA **and are considered treatment-boosted or treatment-emergent,** the IGA score, change in EASI at end of treatment, and titre information will be listed.	To only include data from subjects relevant to be listed.
14.3.16 ~~14.3.12~~ General principles	Summary will include 1st and 3rd quartiles.	To better characterise the summary data for vital signs.
	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 document** will be finalised before breaking the randomisation code.	To further clarify the statistical analysis plan process.
Appendix 8	New appendix added for protocol addendum COVID-19.	Rationale provided in Appendix 8.
Appendix 9	New appendix added for protocol addendum no.2 *Imagine for Studies.*	Rationale provided in Appendix 9.
Throughout	Minor editorial and document formatting revisions.	Minor, have therefore not been summarised.

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List of panels

List of abbreviations

AD	atopic dermatitis
ADA	anti-drug antibody/ (-ies)
ADAM	analysis data model
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
AWS	Amazon Web Services
BP	blood pressure
C_{trough}	trough concentration: lowest concentration reached by a drug before the next dose is administered
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CMO	contract manufacturing organisation
CRA	clinical research associate
CRO	contract research organisation
CSA	cyclosporine A
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	clinical trial report
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI50/75/90	at least 50/75/90% reduction in EASI score
ECG	electrocardiogram
ECZTEND	tralokinumab phase 3 long-term extension trial in subjects with AD who participated in ECZTRA trials (LP0162-1337)
eCRF	electronic case report form
eDiary	electronic diary
EDC	electronic data capture
ePRO	electronic patient-reported outcome

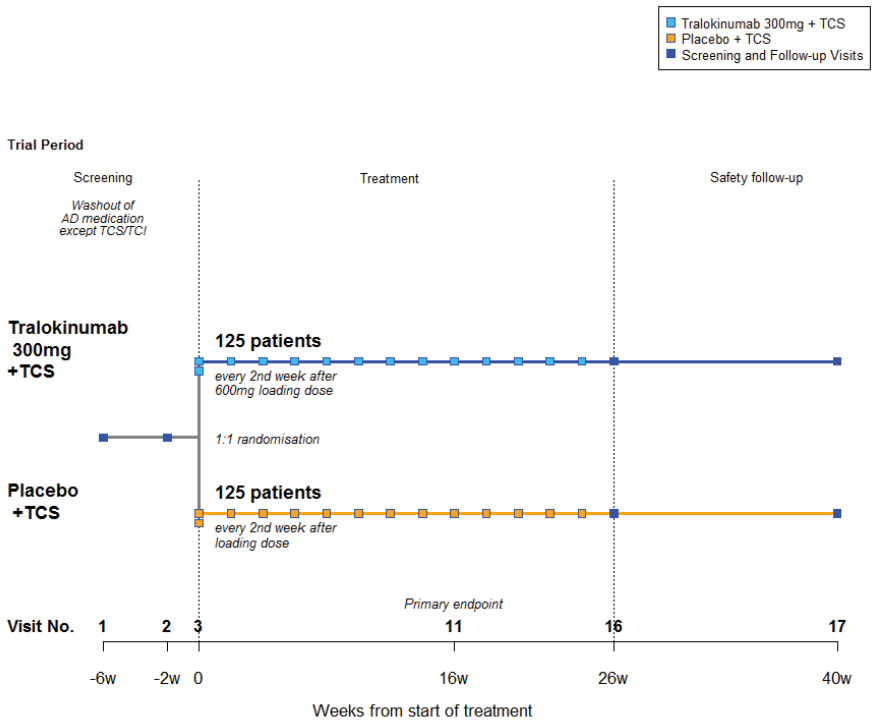
EQ-5D-5L	EuroQoL 5-Dimension Health Questionnaire 5 Level
FAS	full analysis set
FU	follow-up visit
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GPP3	Good Publication Practice standard
HADS	Hospital Anxiety and Depression Scale
HCP	health care professional
HIPAA	Health Insurance Portability and Accountability Act
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
IG	immunoglobulin
IGA	Investigator's Global Assessment
IL	interleukin
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
LEO	LEO Pharma A/S
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
nAB	neutralising antibodies
NBUVB	narrow band ultraviolet B
NRS	numeric rating scale
PDE-4	phosphodiesterase-4
PK	pharmacokinetics
POEM	Patient-Oriented Eczema Measure
PRO	patient-reported outcome
PT	preferred term
PUVA	psoralen + ultraviolet A

Q2W	every other week
SAE	serious adverse event
SC	subcutaneous
SCORAD	Scoring Atopic Dermatitis
SF-36	36-Item Short Form Health Survey
SFU	safety follow-up
SOC	System organ class
TCI	topical calcineurin inhibitors
TCS	topical corticosteroid
Th2	T-helper-2 (cell)
ULN	upper limit of normal
UV A/B	ultraviolet A/B
WHO	World Health Organization

1 Protocol synopsis

Trial ID EudraCT no. IND no.	LP0162-1346 2018-000747-76 123797	
Title of trial	A randomised, double-blind, placebo-controlled, parallel-group, multi-centre, phase 3 trial investigating the efficacy, safety, and tolerability of tralokinumab administered in combination with topical corticosteroids to adult subjects with severe atopic dermatitis who are not adequately controlled with or have contraindications to oral cyclosporine A – ECZTRA 7 (ECZema TRAlokinumab trial no. 7)	
Short title of trial	Tralokinumab in combination with topical corticosteroids in subjects with severe atopic dermatitis who are not adequately controlled with or have contraindications to oral cyclosporine A	
Main objectives and endpoints	Primary objective	Primary endpoint
	To demonstrate that tralokinumab in combination with TCS is superior to placebo in combination with topical corticosteroids (TCS) in treating severe AD in subjects who are not adequately controlled with or have contraindications to oral cyclosporine A (CSA).	At least 75 reduction in EASI score (EASI75)[1] at Week 16
	Secondary objectives	Secondary endpoints
	To evaluate the efficacy of tralokinumab in combination with TCS on severity and extent of AD, itch, and health-related quality of life compared to placebo in combination with TCS.	*Severity and extent of AD* • IGA[2] score of 0 (clear) or 1 (almost clear) at Week 16 • IGA score of 0 (clear) or 1 (almost clear) at Week 26 • Change in SCORAD[3] from baseline to Week 16 • Change in SCORAD from baseline to Week 26 • EASI75 at Week 26 *Itch* • Reduction of Worst Daily Pruritus NRS[4] (weekly average) of at least 4 from baseline to Week 16 • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to Week 26 *Health-related quality of life* • Change in DLQI[5] score from baseline to Week 16

		• Change in DLQI score from baseline to Week 26
	To evaluate the safety of tralokinumab in combination with TCS when treating severe AD in subjects who are not adequately controlled with or have contraindications to oral CSA compared to placebo in combination with TCS.	• Number of adverse events • Presence of anti-drug antibodies (yes/no)
	1 EASI (Eczema Area and Severity Index) 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. 2 IGA (Investigator's Global Assessment) 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). 3 SCORAD (Scoring Atopic Dermatitis) 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 Subjects will assess their worst itch severity over the past 24 hours using an 11-point numeric rating scale ('Worst Daily Pruritus NRS') with 0 indicating 'no itch' and 10 indicating 'worst itch imaginable'. 5 DLQI (Dermatology Life Quality Index) is a validated questionnaire with content specific to those with dermatology conditions. It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their health-related quality of life (HRQoL) over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment. Each item is scored on a 4-point Likert scale (0 = not at all/not relevant; 1 = a little; 2 = a lot; 3 = very much). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor HRQoL.	
Final collection of data for the primary endpoint	Week 16	

Trial design	 **Abbreviations:** AD: atopic dermatitis; No: number; TCI: topical calcineurin inhibitors; TCS: topical corticosteroids; Q2W: every other week; w: week. The trial will consist of a screening period of 6 weeks (Weeks -6 to 0) for washout of previous AD medication (except TCS/TCI), a treatment period of 26 weeks (Weeks 0 to 26), and a 14-week safety follow-up period for the assessment of safety and immunogenicity (Weeks 26 to 40). *Treatment period* Subjects will be randomised in a 1:1 ratio to receive multiple subcutaneous (SC) doses of tralokinumab (300 mg) or placebo every 2 weeks (Q2W) following an initial loading dose of 600 mg on Day 0 (or 4 mL placebo). All subjects will receive TCS (mometasone furoate: Europe class 3 [potent]) to be used as needed throughout the treatment period. The safety and appropriateness of continued or repeated courses of TCS will be monitored and supervised by site staff. Lower potency TCS (Europe class <3) or TCI may be used at the investigator's discretion on areas of the body where the supplied TCS is not advisable. *Safety follow-up* After completion of the treatment periods (at Week 26) or permanent discontinuation of investigational medicinal product (IMP), subjects will enter a 14-week safety follow-up period for assessment of safety and immunogenicity.

	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). On lesional skin, emollients should only be applied at a time where TCS is not applied; on TCS-untreated areas, the emollients may be applied at all times.
Main assessments	Efficacy assessments • IGA • EASI • SCORAD Patient-reported outcomes: 3 patient-reported outcomes (PROs) will be assessed daily using an electronic diary: Eczema-related Sleep NRS, Worst Daily Pruritus NRS, and Patient Days of Topical Treatment Use. 5 PROs will be completed by the subjects at the site during trial visits: The 36-Item Short Form Health Survey (SF-36), Patient-Oriented Eczema Measure (POEM), DLQI, EuroQoL 5-Dimension Health Questionnaire 5 Level (EQ-5D-5L), and Hospital Anxiety and Depression Scale (HADS). Safety assessments Vital signs, physical examination, electrocardiograms, laboratory testing, anti-drug antibodies, and adverse event reporting. Pharmacokinetics
Main criteria for inclusion	• Age 18 and above. • Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD. • History of AD for ≥1 year. • AD involvement of ≥10% body surface area at screening and baseline according to component A of SCORAD. • Subjects who have a recent history (within 1 year before the screening visit) of inadequate response to treatment with topical medications. • Documented history of either no previous CSA exposure and not currently a candidate for CSA treatment OR previous exposure to CSA in which case CSA treatment should not be continued or restarted. • Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.
Main criteria for exclusion	• Subjects for whom TCSs are medically inadvisable e.g., due to important side effects or safety risks. • 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 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	Tralokinumab • 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: 300 mg every 2 weeks (Q2W) following an initial loading dose of 600 mg • Method of administration: Subcutaneous (SC). Placebo • Placebo contains the same excipients in the same concentration only lacking tralokinumab.
Auxiliary medicinal product (AxMP)	TCS (Europe: Class 3 [potent]) Mometasone furoate, 0.1% cream provided in kit sizes of 180–225 g every 2 weeks.
Duration of treatment	Each subject's trial participation will be up to 46 weeks, divided into a screening period (including washout, if applicable) of up to 6 weeks, a treatment period of 26 weeks, and a follow-up period of 14 weeks. Eligible subjects 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 26 under the current protocol).
Number of subjects	A total of 250 subjects will be randomised 1:1 to treatment with tralokinumab 300 mg+TCS or placebo+TCS.
Number and distribution of trial sites	Up to 40 clinical sites in Europe are anticipated. Distribution between countries will be based on feasibility. Inclusion of subjects from Germany is prioritised.
Statistical methods	Analysis of primary endpoint**:** For each of 100 imputed data sets, the difference in response rates between treatment groups will be analysed using the Mantel-Haenszel risk difference stratified by prior CSA use (yes/no) and baseline disease severity (IGA 3 or 4). The estimates and standard errors from the 100 analyses will be pooled to one estimated treatment difference and associated standard error using Rubin's rule to draw inference. From these pooled estimates, the 95% CI for the treatment difference will be calculated. Subjects who prior to the relevant visit receive rescue treatment or permanently discontinue IMP, without prior subject-onset of the COVID-19 pandemic, will be imputed as non-responders. Any missing or collected data from subjects who have subject-onset of the COVID-19 pandemic as their first prior

	intercurrent event will be imputed assuming missing at random (MAR). Data missing prior to any intercurrent event will be handled as non-response, unless data is missing due to the COVID-19 pandemic, in which case it will be imputed assuming MAR. Analysis of secondary efficacy endpoints: Secondary binary endpoints at Week 16 and Week 26 will be analysed as described for the primary endpoint. Secondary continuous endpoints will be analysed using a model for repeated measurements approach with prior CSA use (yes/no), country (Germany: yes/no), baseline disease severity (IGA 3 or 4) and treatment-by-visit interaction as factors and baseline score-by-visit interaction as a continuous covariate. Analysis of secondary safety endpoints: Number of adverse events will be summarised by treatment, system organ class, and preferred term. The frequency of anti-drug antibodies will be summarised by treatment.
Signatory investigator	PPD , Prof. Dr. med PPD , Germany
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

2 Trial identification

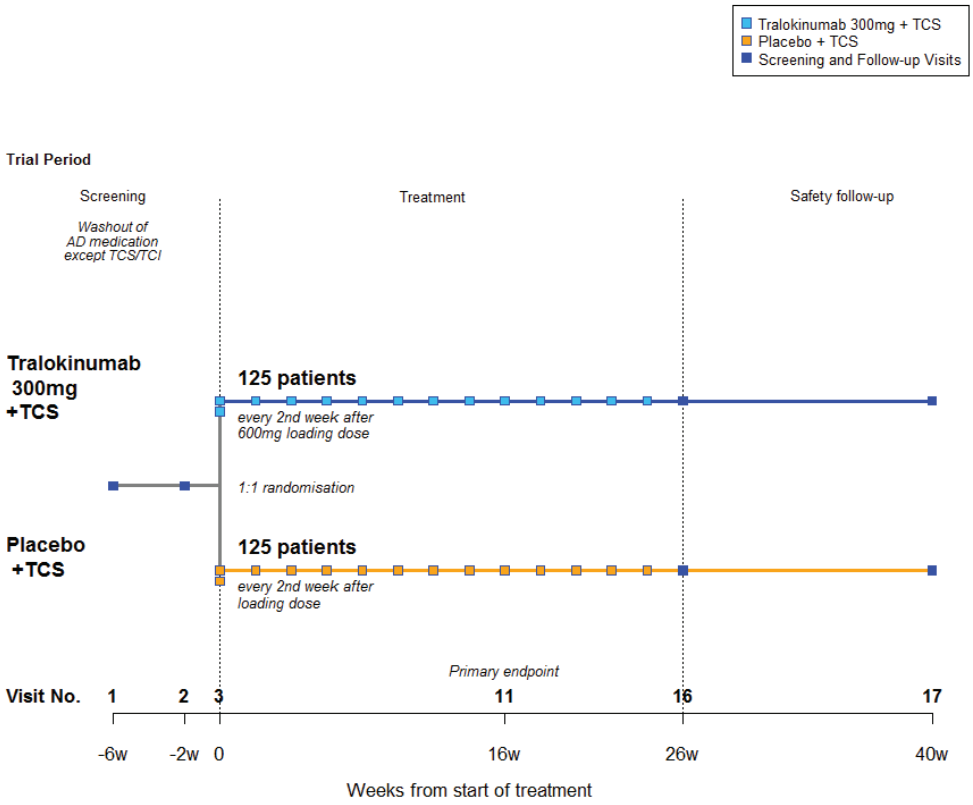
EudraCT number: 2018-000747-76

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



Abbreviations: AD: atopic dermatitis; No: number; TCI: topical calcineurin inhibitors; TCS: topical corticosteroids; Q2W: every other week; w: week.

4 Schedule of trial procedures

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

	Screening		Treatment														Details (protocol sections)
Visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	
Visit window (days)[2]	**±3**	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Trial population and eligibility																	
Informed consent[3]	X																Appendix 3B
Subject eligibility	X		X														8.1 to 8.3
Trial products and randomisation																	
Initiation of emollients (background treatment)[4]		X															9.4
Concomitant medication (including rescue treatment)/ concurrent procedures	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	9.6
Randomisation			X														9.3
IMP administration, compliance			X[5]	X[5]	X[5]	X	X	X	X	X	X	X	X	X	X		9.2
TCS (AxMP) dispensing			X	X	X	X	X	X	X	X	X	X	X	X	X		9.2.2
TCS (AxMP) return				X	X	X	X	X	X	X	X	X	X	X	X	X	9.8.3, 9.8.4
Investigator assessments at baseline																	
C-SSRS	X																11.2.5
Demographics (age), BSA involvement	X		X														11.2.1, 11.2.4
Other demographics and medical history	X																11.2.1, 11.2.2
Height, weight			X														11.2.3
Investigator assessment of efficacy																	
IGA	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	11.3.2
SCORAD	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	11.3.3

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

	Screening		Treatment														Details (protocol sections)
Visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	
Visit window (days)[2]	**±3**	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Subject assessment of efficacy																	
eDiary training		X															
eDiary[6]		<- ========== ->															11.3.4.1 to 11.3.4.3
SF-36			X				X				X					X	11.3.4.4
POEM			X	X	X	X	X		X		X		X			X	11.3.4.5
DLQI			X	X	X	X	X		X		X		X			X	11.3.4.6
EQ-5D-5L			X		X		X		X		X		X			X	11.3.4.7
HADS			X		X		X		X		X		X			X	11.3.4.8
Safety assessments																	
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	11.4.1
Physical examination	X		X				X				X					X	11.4.2
ECG	X		X				X				X					X	11.4.3
Serum pregnancy test, hepatitis B, C, HIV	X																11.4.4
Urine pregnancy test			X		X		X		X		X		X		X	X	11.4.4
Serum chemistry, haematology, IgE	X[7]		X		X		X		X		X		X		X	X	11.4.4
Urinalysis	X		X				X				X				X	X	11.4.4
Anti-drug antibodies			X		X						X					X	11.4.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	13
Other assessments																	
Pharmacokinetics					X						X					X	11.5
Photography[8]			X		X						X					X	11.6.1

1) For subjects who do not require a washout and subjects who only require washout of topical AD treatment (as specified in the exclusion criteria in Section 8.3), 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 planned maximum duration of 6 weeks.
2) If the date of a subject visit does not conform to the trial plan, subsequent visits should be planned to maintain the visit schedule relative to randomisation/baseline.
3) The informed consent form must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations and washout of disallowed medications. Additional informed consent is required for the photography component for the trial sites in scope.
4) All subjects must use an emollient twice daily (or more, as needed) for at least 14 days before randomisation and must continue this treatment throughout the trial (including safety follow-up).
5) For the first 3 IMP dosing visits (visits 3 to 5), subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 30 minutes with vital signs taken every 30 minutes or until stable, whichever is later (see Section 9.2.1).
6) eDiary includes: Eczema-related Sleep NRS, Worst Daily Pruritus NRS, Patient Days of Topical Treatment Use; subjects will complete daily from Week -2 to 26, except for Patient Days of Topical Treatment Use which will be completed daily from Week 0 to 26.
7) IgE not assessed at screening.
8) Optional, selected trial sites only.

Abbreviations: AxMP, auxiliary medicinal product; BSA, body surface area; C-SSRS, Columbia-Suicide Severity Rating Scale; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; eDiary, electronic diary; EQ-5D-5L, EuroQoL 5-Dimension Health Questionnaire 5 Level; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; 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; SF-36, 36-Item Short Form Health Survey; TCS, topical corticosteroid.

Panel 3: Schedule of trial procedures: follow-up including early termination

	Nominal visit[1] (if applicable)		SFU[1,2] (end of trial)	Early termination[1,3] (if applicable)	Unscheduled visit[4] (if applicable)	Details (protocol section)
Visit	**11x**	**16x**	**17**			
Week	**16**	**26**	**40**			
Visit window (days)	**±3**	**±3**	**±3**			
Trial products						
Concomitant medication (incl. rescue treatment)/ concurrent procedures	X	X	X	X	X	9.6
TCS (AxMP) dispensing					X	9.2.2
TCS (AxMP) return				X	X	9.8.3, 9.8.4
Investigator assessment of efficacy						
IGA, EASI	X	X		X	X	11.3.1, 11.3.2
SCORAD	X	X		X	X	11.3.3
Subjects assessment of efficacy						
eDiary[5] completion	X	X		X	X	11.3.4.1 to 11.3.4.3
SF-36	X	X		X	X	11.3.4.4
POEM	X	X		X	X	11.3.4.5
DLQI	X	X		X	X	11.3.4.6
EQ-5D-5L, HADS	X	X		X	X	11.3.4.7, 11.3.4.8
Safety assessments						
Vital signs, physical examination			X	X	X	11.4.1, 11.4.2
ECG			X	X	X	11.4.3
Urine pregnancy test, urinalysis			X	X	X	11.4.4
Serum chemistry, haematology, IgE			X	X	X	11.4.4
Anti-drug antibodies			X	X	X	11.4.5
Adverse events	X	X	X	X	X	13
Other assessments						
Pharmacokinetics			X	X	X	11.5

1) Subjects who permanently discontinue IMP for any reason will be asked to attend all or some of the following additional visits, depending on the timepoint of discontinuation: Visit 11x (16 weeks after randomisation), Visit 16x (26 weeks after randomisation), SFU visit (16 weeks after last administration of IMP), and early termination visit. For further details, please see Section 10.2.1 and Panel 6.
2) All subjects will have a SFU visit 16 weeks after last administration of IMP (which is also considered end-of-trial visit), except subjects who enter the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]) for whom the end-of-trial visit will be the last visit in the present trial before transfer to ECZTEND.
3) Assessments and procedures performed at Week 16 (see Panel 2) are also to be done at an early termination visit.
4) Assessments and procedures to be performed at an unscheduled visit are left at the investigator's discretion.
5) eDiary includes: Eczema-related Sleep NRS, Worst Daily Pruritus NRS, and Patient Days of Topical Treatment Use. Subjects will complete the eDiary daily from Week -2 to 26, except for Patient Days of Topical Treatment Use, which will be completed daily from Week 0 to 26. Subjects who permanently discontinue IMP prior to Week 26 will complete the eDiary daily until the nominal Week 26 visit.

Abbreviations: AxMP, auxiliary medicinal product; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; eDiary, electronic diary; EQ-5D-5L, EuroQoL 5-Dimension Health

Questionnaire 5 Level; 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; SFU, safety follow-up; TCS, topical corticosteroid.

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 is associated with a substantial patient burden that typically includes poor quality of life and sleep disturbance (5).

AD is characterised by an activated T-helper-2 (Th2) pathway with increased expression of key Th2 cytokines including interleukin (IL)-13 (6,7). 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 (6, 8).

IL-13 acts on keratinocytes to release C-C motif chemokine ligand 22 and recruit more IL-13 expressing Th2 cells, decrease differentiation, and contribute to decreased barrier function (9). IL-13 also drives immunoglobulin E (IgE) production and contributes to mast cell activation status and, once allergen cross-links IgE on the cell surface, drives histamine release and induces itch (10, 11). 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 (12).

5.2 Experience with investigational medicinal product

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 (13–15). 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, more than 4,340 subjects have been treated with tralokinumab (cut-off date: 18-Oct-2018) as determined from actual exposure data from completed clinical trials and the enrolment/randomisation schemes for ongoing trials. A phase 3 development programme is ongoing in AD, and other clinical trials with tralokinumab have been conducted in subjects with asthma, ulcerative colitis, idiopathic pulmonary fibrosis, and in healthy subjects. 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.

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 other 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).

5.3 Trial rationale

Treatment recommendations for AD include topical therapies, the main being TCS. Unfortunately, TCS and topical calcineurin inhibitors (TCIs) have limited efficacy in patients with moderate-to-severe disease. TCS and non-biologic systemic therapies (e.g. CSA, azathioprine) are all associated with toxicities with long-term use (16-18). Patients that are unresponsive or unable to use topical treatments or CSA therefore have few treatment options. The recently approved biological agent dupilumab exhibits an acceptable benefit-risk ratio in clinical trials investigating subjects with moderate-to-severe AD, however there is limited experience with long-term dupilumab use in the post-marketing setting.

The primary objective of this trial is to evaluate the efficacy of tralokinumab in combination with TCS compared to placebo in combination with TCS in treating severe AD in subjects who are not adequately controlled with or having contraindications to oral CSA. In addition, secondary endpoints addressing symptom scores and extent of AD (IGA, SCORAD), itch-related sleep loss and itch severity, and health-related quality of life (HRQoL) measures related to AD are also included.

Thus, the trial will contribute to the characterisation of the benefit-risk profile of tralokinumab by considering a more difficult to treat patient population where treatment options are few.

5.4 Justification for dose

The dose selected for the tralokinumab phase 3 development programme is 300 mg Q2W administered subcutaneously. All subjects randomised to treatment with tralokinumab will get an initial loading dose of 600 mg on Day 0 (baseline). The administration of the loading dose of tralokinumab will allow systemic concentrations to reach steady state faster, and potentially reduce the time to onset of clinical effect. The serum concentrations of tralokinumab after the 600 mg loading dose will not exceed the serum tralokinumab concentrations at steady state for the 300 mg Q2W.

The tralokinumab 300 mg Q2W dose was chosen based on the results of the phase 2b trial in subjects with moderate-to-severe AD (trial D2213C00001) described in Section 5.2. The subjects were treated with 3 different fixed dose regimens of tralokinumab (45, 150, or 300 mg Q2W) or placebo to evaluate safety and efficacy over a treatment period of 12 weeks. In the overall intention-to-treat phase 2b population, a statistically significant improvement in EASI change from baseline at Week 12 was observed in the tralokinumab 300 mg group versus placebo; however, formal statistical significance was not demonstrated for the co-primary endpoint IGA. The key secondary and exploratory endpoint results from trial D2213C00001 also supported the selection of the tralokinumab Q2W 300 mg dose for phase 3 development; and overall, larger numerical differences were observed for 300 mg tralokinumab dose than for 150 mg compared to placebo for most of the trial endpoints.

Since the safety profile in trial D2213C00001 was acceptable in all treatment cohorts and no clear safety-related dose-response pattern was identified, the dose of 300 mg Q2W has been selected for evaluation in the phase 3 development programme for tralokinumab in AD.

5.5 Ethical considerations

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

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

In this trial in adult subjects with severe AD who are otherwise healthy, the efficacy of tralokinumab in combination with TCS therapy will be compared with a placebo control group on TCS therapy. The choice of placebo (on the background of TCS) as control is appropriate for addressing the objectives of this trial and it will provide information regarding treatment with tralokinumab in combination with TCS. Subjects will be under supervision by a dermatologist or allergist every second week for the duration of the treatment period, which is more frequent than standard clinical practice. All subjects will be treated with TCS (Europe: Class 3 [potent]) as needed, and rescue treatment may be given to the subjects at the investigator's discretion for the duration of the trial.

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

In accordance with the current version of the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, qualified medical personnel employed by LEO will be readily available to advise on trial-related medical questions. Medical monitoring will be performed throughout the trial and safety data will be reviewed regularly by medically qualified staff at LEO to ensure that prompt action is taken, if needed, to maximise patient safety. In conclusion, the trial design chosen is regarded as ethically justified and adherent with ethical requirements.

5.6 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. 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 severe AD who are not adequately controlled with or have contraindications to oral CSA.

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 anti-drug antibodies (ADA) have been detected in very few subjects exposed to tralokinumab for up to one year. 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 treatment period) as a precautionary measure against hypersensitivity reactions (further details are given in Section 9.2).
- 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 [20]).
- 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

Panel 4: Objectives and endpoints

Objectives	Endpoints
Primary objective	Primary endpoint
To demonstrate that tralokinumab in combination with TCS is superior to placebo in combination with TCS in treating severe AD in subjects who are not adequately controlled with or have contraindications to oral CSA	• EASI75 at Week 16
Secondary objective	Secondary endpoints
To evaluate the efficacy of tralokinumab in combination with TCS on severity and extent of AD, itch, and health-related quality of life compared to placebo in combination with TCS	*Severity and extent of AD* • IGA score of 0 (clear) or 1 (almost clear) at Week 16 • IGA score of 0 (clear) or 1 (almost clear) at Week 26 • Change in SCORAD from baseline to Week 16 • Change in SCORAD from baseline to Week 26 • EASI75 at Week 26 *Itch* • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to Week 16 • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to Week 26 *Health-related quality of life* • Change in DLQI score from baseline to Week 16 • Change in DLQI score from baseline to Week 26
To evaluate the safety of tralokinumab in combination with TCS when treating severe AD in subjects who are not adequately controlled with or having contraindications to oral CSA compared to placebo in combination with TCS	• Number of AEs • Presence of ADA (yes/no)

Objectives	Endpoints
Other objectives	Other endpoints
To support the primary and secondary objectives in the trial	*Supporting primary endpoint* • EASI90 at Week 16 • Change from baseline to Week 16 in EASI score • Percent change from baseline to Week 16 in EASI score *Supporting secondary endpoints related to the severity and extent of AD* • EASI90 at Week 26 • Change from baseline to Week 26 in EASI score • Percent change from baseline to Week 26 in EASI score • Percent change from baseline to Week 16 in SCORAD • Percent change from baseline to Week 26 in SCORAD *Supporting the secondary endpoint related to itch* • Change from baseline to Week 16 in Worst Daily Pruritus NRS (weekly average) • Percent change from baseline to Week 16 in Worst Daily Pruritus NRS (weekly average) • Change from baseline to Week 26 in Worst Daily Pruritus NRS (weekly average) • Percent change from baseline to Week 26 in Worst Daily Pruritus NRS (weekly average) • Change from baseline to Week 16 in Eczema-related Sleep NRS (weekly average) • Percent change from baseline to Week 16 in Eczema-related Sleep NRS (weekly average) • Change from baseline to Week 26 in Eczema-related Sleep NRS (weekly average) • Percent change from baseline to Week 26 in Eczema-related Sleep NRS (weekly average) *Supporting the secondary endpoint related to health-related quality of life* • Reduction from baseline to Week 16 of DLQI of ≥4 points among subjects with baseline DLQI ≥4 • Reduction from baseline to Week 26 of DLQI of ≥4 points among subjects with baseline DLQI ≥4

Objectives	Endpoints
To evaluate the efficacy of tralokinumab in combination with TCS on patient-reported outcomes compared to placebo in combination with TCS.	• Change from baseline to Week 16 in SF-36 score • Change from baseline to Week 26 in SF-36 score • Change from baseline to Week 16 in POEM • Change from baseline to Week 26 in POEM • Reduction from baseline to Week 16 of POEM of ≥4 points among subjects with baseline POEM ≥4 • Reduction from baseline to Week 26 of POEM of ≥4 points among subjects with baseline POEM ≥4 • Change from baseline to Week 16 in EQ-5D-5L score • Change from baseline to Week 26 in EQ-5D-5L score • Change from baseline to Week 16 in EQ-5D-5L VAS score • Change from baseline to Week 26 in EQ-5D-5L VAS score • Change from baseline to Week 16 in HADS • Change from baseline to Week 26 in HADS • HADS-anxiety and HADS-depression scores < 8 at Week 16 • HADS-anxiety and HADS-depression scores < 8 at Week 26 • Change from baseline to Week 16 in HADS-anxiety score • Change from baseline to Week 26 in HADS-anxiety score • Change from baseline to Week 16 in HADS-depression score • Change from baseline to Week 26 in HADS-depression score
To evaluate the efficacy of tralokinumab in combination with TCS on health care resource utilisation compared to placebo with TCS.	• Amount of TCS used from baseline to Week 16 • Amount of TCS used from baseline to Week 26 • Number of days without topical treatment use from baseline to Week 16 • Number of days without topical treatment use from baseline to Week 26

Abbreviations: AD, atopic dermatitis; ADA, anti-drug antibodies; CSA, cyclosporine A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI75/90, at least 75/90% reduction in EASI score; EQ-5D-5L, EuroQoL 5-Dimension Health Questionnaire 5 Level; HADS, Hospital Anxiety and Depression Scale IGA, Investigator's Global Assessment; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; SF-36: Short Form-36 questionnaire; TCS, topical corticosteroids.

7 Trial design

7.1 Overall trial design

Overview

This is a randomised, double-blind, placebo-controlled, parallel-group, multi-centre, phase 3 clinical trial in adult subjects with severe AD ineligible to treatment with CSA. The trial will consist of a screening period, a treatment period, and a safety follow-up period. The primary endpoint is assessed at Week 16, and the final efficacy assessment will be conducted at Week 26.

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

Screening period (Week -6 to Week 0)

The screening period has a minimum duration of 2 weeks and a planned maximum duration of 6 weeks. The exact duration of the screening period for the individual subject depends on the length of any washout 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 topical PDE-4 inhibitors.

If no washout or a 2-week washout period is required, screening will be reduced to 2 weeks and reduced to 1 visit (Week -2; visit 2), i.e., the 2 planned 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. On lesional skin,

emollients should only be applied at a time where TCS is not applied; on TCS-untreated areas, the emollients may be applied at all times.

Treatment period (Week 0 to Week 26)

Following the screening period, approximately 250 subjects will be randomised 1:1 to one of the following groups stratified by prior CSA use (yes/no), country (Germany: yes/no), and baseline disease severity (IGA 3 or 4):

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

The last dose of IMP will be administered at Week 24.

Subjects in both treatment groups will apply a thin film of a supplied TCS once daily to areas with active lesions as needed; lower potency TCS or TCI may be prescribed if needed on body areas where the supplied TCS is not advisable or on areas where continued treatment with TCS is considered unsafe. Topical therapy will be discontinued when control is achieved; discontinuation should preferably be gradual. The safety and appropriateness of continued or repeated courses of TCS therapy will be monitored and supervised by the site staff.

Safety follow-up period (Week 26 to Week 40)

Subjects, except those who enter the long-term extension trial (LP0162-1337, ECZTEND, see below), will complete a 14-week off-treatment follow-up period for the assessment of safety, PK, and ADA.

Long-term extension trial (selected countries)

Eligible subjects 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 26 under the current protocol).

7.2 Number of subjects needed

Assuming a screening failure rate of 25%, approximately 333 subjects will be screened and approximately 250 subjects will be randomly assigned 1:1 to tralokinumab 300 mg+TCS or placebo+TCS. 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 40 sites in Europe. The anticipated minimum number of randomised subjects per trial site is 4 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 40. Subjects entering the long-term extension trial (LP0162-1337, ECZTEND) after completion of the end-of-treatment visit (Week 26) 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 30-Mar-2018 (or later) 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 (or newer) 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.

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 eCRF if the subject has met all the inclusion criteria and none of the exclusion criteria.

Any implementation of national requirements/law for the subject's participation in the clinical trial will be ensured and described in submission documentation to regulatory authorities and IRBs/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.
2. Age 18 and above.
3. Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD (21; Appendix 4)
4. History of AD for ≥1 year.
5. Subjects who have a recent history (within 1 year before the screening visit) of inadequate response to treatment with topical medications.
    - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to higher potency (±TCI as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent TCS), whichever is shorter.
    - Subjects with documented systemic treatment for AD in the past year are also considered as inadequate responders to topical treatments and are potentially eligible for treatment with tralokinumab after appropriate washout.

6. AD involvement of ≥10% body surface area at screening and baseline according to component A of SCORAD.

7. EASI score ≥20 at screening and baseline
8. An IGA score of ≥3 at screening and at baseline
9. A Worst Daily Pruritus numeric rating scale (NRS) average score of ≥4 during the week prior to baseline.

    - Worst Daily Pruritus NRS score at baseline will be calculated from daily assessments of worst itch severity (Worst Daily Pruritus NRS) during the 7 days immediately preceding randomisation (Day -6 to 0). A minimum of 4 Worst Daily 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.

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

11. Women of child-bearing potential must use a highly effective* form of birth control (confirmed by the investigator) throughout the trial and at least for 16 weeks (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). The subjects must have used the contraceptive method continuously for at least 1 month prior to the pregnancy test at baseline. A female is defined as not being of child-bearing potential if she is postmenopausal (at least 12 months with no menses without an alternative medical cause prior to screening), or surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

12. Documented history by a physician of either:

- No prior CSA exposure and not currently a candidate for CSA treatment due to any of the following:
    i. medical contraindications (e.g., uncontrolled hypertension on medication) or hypersensitivity to CSA active substance or excipients
    ii. use of prohibited concomitant medications (e.g., statins, digoxin, macrolide, antibiotics, barbiturates, anti-seizure, non-steroidal anti-inflammatory drugs, diuretics, angiotensin-converting-enzyme inhibitors, St John's Wort)
    iii. increased susceptibility to CSA-induced renal damage (elevated creatinine) and liver damage (elevated function tests), or increased risk of serious infections
- Previously exposed to CSA, and CSA treatment should not be continued or restarted due to any of the following:
    i. intolerance or unacceptable toxicity (e.g., elevated creatinine, elevated liver function tests, uncontrolled hypertension, paraesthesia, headache, nausea, hypertrichosis)
    ii. inadequate response to CSA (defined as flare of AD on CSA tapering after a maximum of 6 weeks of high dose [5 mg/kg/day] to maintenance dose [2 to 3 mg/kg/day] or a flare after a minimum of 3 months on maintenance dose). Flare is defined as increase in signs or symptoms leading to escalation of therapy, which can be an increase in dose, a switch to a higher potency class of TCS, or the start of another systemic non-steroidal immunosuppressive drug
    iii. requirement for CSA at doses >5 mg/kg/day, or duration beyond those specified in the prescribing information (>1 year)

8.3 Exclusion criteria

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

1. Subjects for whom TCS are medically inadvisable e.g., due to important side effects or safety risks (including intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects etc.) in the opinion of the investigator.
2. Concurrent enrolment in another interventional clinical trial.

3. Previous randomisation in a tralokinumab clinical trial.
4. Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis.
5. Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD.
6. Use of tanning beds or phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]), within 6 weeks prior to randomisation.
7. Treatment with the following medications within 4 weeks prior to randomisation:
    - Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, CSA, azathioprine, mycophenolate mofetil, Janus kinase inhibitors).
    - Systemic corticosteroid use (excludes topical, inhaled, or intranasal delivery).
    - Three or more bleach baths during any week within the 4 weeks.
8. Treatment with topical 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.
    - Receipt of inactive/killed vaccinations (e.g. inactive influenza) is allowed, provided they are not administered within 5 days before/after any trial visit.
10. Receipt of any marketed biological therapy (i.e. immunoglobulin, anti-IgE) including dupilumab or investigational biologic agents:
    - Any cell-depleting agents including but not limited to rituximab: within 6 months prior to randomisation, or until lymphocyte count returns to normal, whichever is longer.
    - Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to randomisation.
11. Receipt of any investigational non-biologic agent within 5 half-lives prior to randomisation.
12. Receipt of blood products within 4 weeks prior to screening.

13. Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.
14. Known or suspected allergy or reaction to any component of the IMP or AxMP formulation.
15. History of any active skin infection within 1 week prior to randomisation.
16. History of a clinically significant infection within 4 weeks prior to randomisation which, in the opinion of the investigator or sponsor's medical expert, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial. Clinically significant infections are defined as:
    - a systemic infection.
    - a serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication.
17. A helminth parasitic infection within 6 months prior to the date informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy.
18. History of anaphylaxis following any biological therapy.
19. History of immune complex disease.
20. History of cancer:
    - Subjects who have had basal cell carcinoma, localised squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained.
    - Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained.
21. Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care.

22. History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at screening, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.
23. History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
24. History of attempted suicide or at significant risk of suicide (either in the opinion of the investigator or defined as a "yes" to suicidal ideation questions no. 4 or 5 or answering "yes" to suicidal behaviour on the Columbia-Suicide Severity Rating Scale [C-SSRS] Screening version).
25. Any disorder, including but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, psychiatric, or major physical impairment that is not stable, in the opinion of the investigator, and could:
    - Affect the safety of the subject throughout the trial.
    - Influence the findings of the trial or their interpretations.
    - Impede the subject's ability to complete the entire duration of trial.
26. Any clinically significant abnormal findings in physical examination, vital signs, electrocardiogram (ECG), haematology, clinical chemistry, or urinalysis during the screening period, which in the opinion of the investigator, may put the subject at risk because of his/her participation in the trial, or may influence the results of the trial, or the subject's ability to complete entire duration of the trial.
27. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.0 times the ULN (upper limit of normal) at screening.
28. Positive hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) or hepatitis C virus antibody (anti-HCV) serology at screening. Subjects with positive HBsAb may be randomised provided they have a history of hepatitis B vaccination and have negative HBsAg and HBcAb serology.
29. Subjects who are not willing to abstain from donating blood and/or plasma from the time of informed consent and for 16 weeks (5 half-lives) after last dose of IMP.
30. Subjects who are legally institutionalised.
31. Pregnant, breastfeeding, or lactating women.

32. Employees of the trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.

8.4 Screening and screening failures

Subject identification number

Trial participation begins once written informed consent is obtained. Refer to Appendix 3B for details on the informed consent process. Once informed consent is obtained, a subject identification number (subject ID) will be assigned by 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 who have given written informed consent to participate in the trial and who have been assigned a subject ID are considered 'screened' subjects.

The investigator will maintain a log of all 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 they have provided written informed consent or not (screening log). This log will be anonymous and will include the reason(s) for not entering the trial, if applicable, or the allocated subject ID.

Screening failures

Screening failures are defined as subjects who consent to participate in the trial but are not subsequently randomly assigned to trial treatment. A minimal set of screening failure information is required to ensure transparent reporting of screening failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (22) and to respond to queries from regulatory authorities. The following data will be collected in the eCRF for screening failures:

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

- Date of informed consent.
- Demographics (age, sex, race, and ethnicity).
- Reason for screen failure:
    - Failure to meet randomisation criteria.
    - Lost to follow-up.
    - Withdrawal by subject.

- Other.

- Date of screen failure.
- Any 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

9.1.1 Investigational medicinal product (IMP)

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 5 for further details).

Panel 5: Identification of IMPs

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.

9.1.2 Auxiliary medicinal product (AxMP)

Each subject will be prescribed an auxiliary medicinal product (AxMP): the subjects will receive a TCS cream (Europe: Class 3 [potent]) from randomisation (Week 0) to Week 26. This will be provided as mometasone furoate, 0.1% cream in kit sizes of 180–225 g every 2 weeks. This should be the only TCS product applied to the body during this period, excluding areas of the body where the supplied TCS is not advisable or where continued use is considered unsafe (see Section 9.2.2 for further details).

9.2 Administration of trial products

9.2.1 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 24. To ensure blinding, both treatment groups will receive the same number of injections at each visit.

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 treatment period, each subject will receive 2 SC injections (each of 1 mL).

Hence, subjects in the treatment period will receive either:

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

IMP will be administered by a qualified, unblinded health care 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 the trial product handling manual. IMP administration must be carried out according to these instructions.

After IMP administration

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

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

(mediated by an immunologic mechanism) and nonallergic anaphylaxis (which has a nonimmunologic cause) (23). The clinical criteria for defining anaphylaxis for this trial are listed in Appendix 5. 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.

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

9.2.2 Administration of AxMP

The IRT will assign the required AxMP (TCS) kit numbers for each subject at each dispensing visit. The TCS will be provided as mometasone furoate, 0.1% cream in kit sizes of 180–225 g Q2W. If needed, additional TCS kit(s) may be dispensed to the subject at a scheduled or unscheduled visit at the investigator's discretion. The amount of additional TCS dispensed must be recorded in the eCRF.

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

From randomisation (Week 0) and until last administration (at Week 24), the TCS will be dispensed and the subject must return used and unused TCS tubes at each subsequent trial visit, to assess the amount of medication used. The subjects must be instructed by the site staff on the importance of returning all used and unused TCS tubes. The site staff will return used and unused TCS tubes to the contract manufacturing organisation (CMO). The TCS tubes will be weighed at the CMO before shipment to the trial sites and again upon return.

An additional, lower potency TCS or TCI may be used at the investigator's discretion on areas of the body where use of the supplied TCS is not advisable such as areas of thin skin (face, skin fold areas, genital areas, etc.) or on areas where continued treatment is considered unsafe. The lower potency TCS and TCI will not be provided by LEO and will not be weighed, but must be registered in the eCRF as concomitant medications (see Section 9.6).

Further details on TCS dispensing are provided in the trial product handling manual. TCS administration must be carried out according to these instructions.

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+TCS or placebo+TCS, stratified by prior CSA use (yes/no), country (Germany: yes/no), and baseline disease severity (IGA 3 or 4).

The IRT will be used to control randomisation and stratification factors, along with trial product 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 the investigator or LEO staff who are involved in the treatment or clinical evaluation and monitoring of the subjects will be aware of the treatment received.

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

Since tralokinumab and placebo are visually distinct and not matched for viscosity, IMP will be handled and administered by a qualified, unblinded HCP (trained site staff) at the site who

will not be involved in the management of trial subjects and who will not perform any of the assessments.

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

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 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. If possible, investigators should attempt to limit the first step of rescue therapy to topical medications (i.e. higher potency TCS, Europe class >3), and escalate to systemic medications only for subjects who do not respond adequately after at least 14 days of topical treatment. The subject will be monitored for signs of local or systemic TCS toxicity and the safety and appropriateness of continued use will be supervised by site staff.

Subjects who receive topical rescue treatment (higher potency TCS, Europe class >3) will continue IMP treatment.

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

Investigators should make every attempt to conduct efficacy and safety assessments (at least disease severity scores [IGA and EASI], concomitant medications/ procedures, and AEs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose, if necessary. In the primary efficacy analyses, subjects who receive higher potency TCS (Europe Class >3) or systemic rescue treatment during the treatment period will be considered as non-responders.

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 40) 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 40):

- 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 listed below are prohibited during the trial from randomisation. Medications and procedures disallowed prior to randomisation are covered in the exclusion criteria (see Section 8.3). In case any prohibited treatments are used during the trial, they must be recorded as concomitant medication.

From randomisation through end of treatment (Week 26):

- PDE-4 inhibitors.
- TCS of higher potency (Europe class >3).
- Use of UVA or UVB, psoralen + UVA (PUVA), other phototherapy, or tanning beds.
- 3 or more bleach baths per week.

From randomisation through safety follow-up (Week 40):

- Investigational agents other than tralokinumab.

- Systemic corticosteroids (nasal and inhaled corticosteroids are allowed).
- Systemic treatment for AD with an immunosuppressive/immunomodulating agent (examples include: cyclosporine A, mycophenolate mofetil, azathioprine, methotrexate, Janus kinase inhibitors, interferon-gamma, dupilumab, or other biologics).

In case prohibited systemic medications are received (for any indication), 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 40):

- Allergen immunotherapy.
- Live (attenuated) vaccine.
- Immunoglobulins.
- Blood products.

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

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

Investigational medicinal product
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.

Auxiliary medicinal product
The AxMP (TCS) will be packaged in individually numbered kits that contain tubes of TCS cream with a total weight of 180–225 g. Primary and secondary packaging materials (tube and outer kit carton, respectively) will be individually labelled.

The labelling of AxMPs 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

Storage of IMP
All LEO 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 (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 trial product handling manual.

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

The TCS must be stored at the site according to the approved label for mometasone furoate. The temperature during storage must be recorded 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 TCS 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 TCS 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 TCS should be documented via IRT (refer to the IRT instructions for further details) and reported as a product complaint to Global Safety, LEO (see Section 9.10). Damaged TCS should not be used.

9.8.3 Drug accountability

Trial product accountability will be performed in the IRT.

IMP 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.

Individual drug accountability of the IMP administered to each subject randomised in the trial must be documented. The individual drug accountability must be available during monitoring visits and will be checked by the CRA to verify correct dispensing of the IMP. Drug accountability information will be entered in the IRT, where also inventory status of all IMP at the trial site will be maintained. For more information about IMP and AxMP accountability, please refer to the trial product handling manual.

The IMPs must be fully accounted for by the CRA with the help of site staff responsible for dispensing the IMPs. All unused IMPs supplied by the CMO on behalf of LEO will be returned to the CMO.

AxMP accountability

The number of TCS tubes returned by the subject must be documented in the eCRF by the trial staff. The subject will at each dispensing visit return used, partly used, and unused TCS tubes (including empty kit cartons) to the site. Once reconciled and accounted for, the site will return all of the above to the CMO. For further details, please see the trial product handling manual.

All returned AxMP tubes will be weighed by the CMO to determine the amount of TCS used by the subject. The detailed procedure for weighing of AxMP tubes and subsequent transfer of tube weight data to the clinical database will be documented.

Reporting in eCRF

The IMP kit numbers as well as the date and time of IMP administration will be recorded in the eCRF. In addition, the site of IMP injection should be given. For AxMP (TCS), the kit/tube number, date of dispensation and return, and number of tubes dispensed and returned will be recorded in the eCRF.

9.8.4 Treatment compliance

IMP injections will be performed by site staff that will also hand out TCS for self-administration and keep the accountability records up to date. Any non-compliance with IMP administration and dispensing and return of TCS and the reason for it must be recorded in the eCRF.

9.8.5 Trial product destruction

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

9.9 Provision for subject care following trial completion

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

9.10 Reporting product complaints

Any defects or issues with the IMP, AxMP (TCS) as well as any IMP device deficiency (including malfunctions, use errors, and inadequate labelling) must be reported to Global Safety at LEO 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 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. Similarly, any defects or issues with TCS must be reported to Global Safety using the same complaint procedure as for the IMP and device.

Refer to the IRT training 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 contact information for reporting product complaints:

Fax number: +45 7226 3287

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

10 Discontinuation and withdrawal

10.1 General principles

A subject may 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 investigator, or LEO considers that it is not in the subject's best interest to continue.

In order to obtain the most representative efficacy evaluation of tralokinumab, it is key to assess the efficacy status of each trial participant at the planned primary and secondary endpoints (nominal Week 16 and 26 visits), irrespective of whether the subject has discontinued IMP or not (see Panel 2). Hence, permanent discontinuation of IMP and withdrawal from trial are considered to be (potentially) 2 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 10.3 (see Panel 6 for additional visits required following permanent discontinuation of IMP).
- **Withdrawal from trial** occurs when stop of all trial activities takes place before the last planned safety follow-up visit (Week 40). 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).

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., 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 additional visits as indicated below (Panel 6). See the schedule of trial procedures for data to be collected at these visits (Section 4). The investigator will review any AEs which will be followed up according to Section 13.7, if the subject agrees.

Panel 6: Additional visits after permanent discontinuation of IMP

IMP discontinuation stage	Additional visits required
Prior to Week 16	• Early termination visit • Nominal Week 16 visit (16 weeks after randomisation) • Nominal Week 26 visit (26 weeks after randomisation) • Final SFU visit (16 weeks after last administration of IMP)
After Week 16 and prior to Week 26	• Early termination visit • Nominal Week 26 visit (26 weeks after randomisation) • Final SFU visit (16 weeks after last administration of IMP)
After Week 26 and prior to Week 40	• Early termination visit • Final SFU visit (16 weeks after last administration of IMP)

Abbreviations: IMP, investigational medicinal product; SFU, safety follow-up.

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 and medical records

The reason for permanent discontinuation of IMP must be recorded in the medical records and in the eCRF (on the end-of-treatment form and end-of-trial form). The reason for subject withdrawal must be recorded in the medical records and in the eCRF (end-of-trial form). For subjects who do not attend the nominal visits at Week 16 or Week 26 or the safety follow-up visit, the reason for not attending will be recorded in the medical records and in the eCRF.

The categories for assigning reasons in the eCRF are: 'lack of efficacy', 'AE', 'withdrawal by subject', 'lost to follow-up', 'death', or 'other'. If 'AE' 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 (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

11 Trial assessments and procedures

11.1 Overview

During the trial there are 17 scheduled site visits at the clinic. 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 treatment.
- Panel 3 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 order assigned below:

- PROs:
    - DLQI
    - EQ-5D-5L
    - POEM
    - HADS
    - SF-36
- Investigator assessments/procedures:
    - SCORAD component C, then component A and B
    - IGA
    - EASI
- Safety and laboratory assessments (including PK)
- Other assessments (photographs)
- Administration of IMP

Subjects may also need to be seen at unscheduled visits during the course of the trial. The assessments performed at an unscheduled visit are left at the investigator's discretion, except if the unscheduled visit involves administration of rescue treatment. In that case, the investigator should make every attempt to conduct efficacy and safety assessments (at least disease severity scores [IGA and EASI], concomitant medications/procedures, and AEs) immediately before administering any rescue treatment. An unscheduled visit may include any assessment performed at an early termination visit, see Panel 3 for details.

Subjects participating in the trial will be under careful supervision of a qualified principal investigator (see Appendix 1.4). 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: date of birth (or only year and month of birth as applicable according to local legislation).
- Sex: female; male.
- Race: American Indian or Alaska native; Asian; black or African American; native Hawaiian or other Pacific islander; white; or other. If 'other' is selected as race, a further specification needs to be provided in the eCRF.
- 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 Height and weight

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

11.2.4 Body surface area involvement

The total body surface area (BSA) 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 trial procedures (Section 4).

11.2.5 Columbia-Suicide Severity Rating Scale

The C-SSRS is a rater-administered instrument used to assess the lifetime history and severity of suicidal ideation and suicidal behaviour through a series of simple, plain-language questions (24, 25). The C-SSRS must be completed at the screening visit to check that

exclusion criterion no. 24 does not apply. Further details on the assessment according to the C-SSRS are included in the efficacy assessment & C-SSRS manual.

11.3 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 7; 26). 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 7: 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 (27). The EASI score will be assessed according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. 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 8. 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 9. For each body region, a severity sum score will be calculated which will be multiplied by an area score (Panel 9) and by a weighting factor. The EASI score equals the sum of the scores obtained for each body region (Panel 8).

Panel 8: 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 (28).

Panel 9: 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 (28). 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

All PROs included in this trial are included in the investigator trial file.

11.3.4.1 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 26.

11.3.4.2 Worst Daily Pruritus numeric rating scale

Subjects will assess their worst itch severity over the past 24 hours using an 11-point NRS ('Worst Daily Pruritus NRS') with 0 indicating 'no itch' and 10 indicating 'worst itch imaginable'. Subjects will complete the Worst Daily Pruritus NRS as part of an eDiary each day in the morning from Week -2 (visit 2) until Week 26.

11.3.4.3 Patient Days of Topical Treatment Use

Subjects will assess their use of topical AD treatment over the past 24 hours using a response scale ('yes', 'no'). Subjects will complete the Patient Days of Topical Treatment Use as part of an eDiary each day in the morning from baseline (Week 0 [visit 3]) until Week 26.

11.3.4.4 SF-36

The SF-36 (version 2, Acute Recall) is a 36-item general health status assessment. Subjects will be asked to answer each question by selecting one of 3 to 6 categorical response options. The instrument instructions do not state a specific recall period; however, a recall period is defined within most items. The acute recall version, which asks subjects about the last week, will be used in this trial (30).

The SF-36 (version 2) yields scores for 8 health domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) and 2 psychometrically derived summary scores (a physical component summary and a mental component summary).

The SF-36 will be completed electronically on the device supplied to the trial site according to the schedule of trial procedures in Section 4.

11.3.4.5 Patient-Oriented Eczema Measure

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

11.3.4.6 Dermatology Life Quality Index

The DLQI is a validated questionnaire with content specific to those with dermatology conditions. It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their HRQoL over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment (32). Each item is scored on a 4-point Likert scale (0 = 'not at all/not relevant'; 1 = 'a little'; 2 = 'a lot'; 3 = 'very much'). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor HRQoL. The DLQI will be completed electronically on the device supplied to the trial site according to the schedule of trial procedures (Section 4).

11.3.4.7 EQ-5D-5L

The EQ-5D-5L is a standardised measure of health status developed by the EuroQoL group to provide a simple, generic measure of health for clinical and economic appraisal (33). The EQ-5D-5L is a self-administered questionnaire used to assess health status 'today' and is divided into 2 sections: The first section includes 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression); each dimension will be assessed by the subject using a 5-point scale ('no problems', 'slight problems', 'moderate problems', 'severe problems', and 'extreme problems'). The second section consists of a vertical visual analogue scale anchored at 0 ('the worst health you can imagine') and 100 ('the best health you can imagine'). The EQ-5D-5L will be completed electronically on the device supplied to the trial site according to the schedule of trial procedures (Section 4).

11.3.4.8 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 (34). 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 trial procedures (Section 4).

11.4 Safety assessments

11.4.1 Vital signs

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

For the first 3 IMP dosing visits (i.e., Weeks 0, 2, and 4), subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 30 minutes with vital signs taken at 30 minutes or until stable, whichever is later (Section 9.2.1).

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

In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later with subjects resting in a supine 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. 26).

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

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. 26); 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 10 will be performed.

Panel 10: Clinical laboratory tests

Chemistry	Haematology
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bilirubin[1] Calcium Cholesterol Creatinine Gamma glutamyl transferase Glucose (non-fasting) HDL cholesterol Lactate dehydrogenase LDL cholesterol Potassium Protein Sodium Triglycerides Tryptase[2] Urea nitrogen	Basophils Basophils/leucocytes Eosinophils Eosinophils/leucocytes Erythrocyte mean corpuscular haemoglobin concentration Erythrocyte mean corpuscular volume Erythrocytes Haematocrit Haemoglobin Leucocytes Lymphocytes Lymphocytes/leucocytes Monocytes Monocytes/leucocytes Neutrophils Neutrophils/leucocytes Thrombocytes
Urinalysis	**Serology**
Glucose Ketones Leukocytes Nitrite Occult blood Protein	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.
5) Only female subjects of child-bearing 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. 26, 27, and 28).

A serum pregnancy test must be taken at the screening visit in female subjects of child-bearing 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 child-bearing 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').

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 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 the 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 Other assessments

11.6.1 Photography

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

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

Digital colour photographs will be taken of the disease area and representative lesions at 4 different time points according to the schedule of trial procedures (Section 4).

Custom photography equipment will be delivered to trial sites by the central photography vendor together with a photography manual. Photography standards and procedures are provided in the manual. The photographs will have no other subject identifier than the subject ID and will be transmitted electronically to the photography vendor using a secure file transfer protocol.

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

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

11.7 Estimate of total blood volume collected

Blood samples will be drawn for haematology, biochemistry, serology, PK, and ADA. The total volume of blood to be drawn is approximately 160 mL, which is less than the volume of blood drawn during a blood donation (approximately 500 mL).

11.8 End of trial

An end-of-treatment form and an end-of-trial form will be completed in the eCRF for all randomised subjects, including subjects who permanently discontinue IMP and subjects who withdraw from the trial (see Section 10.3 for early termination assessments).

End-of-treatment form

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

End-of-trial form

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, AE, withdrawal by subject, lost to follow-up, death, other).
- Did the subject attend the nominal Week 16 and 26 visits. If not, the primary reason for not attending the visit must be recorded (lack of efficacy, AE, withdrawal by subject, 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, AE, withdrawal by subject, lost to follow-up, death, other).
- Date of last contact.

If 'AE' or 'other' is selected, a specification must be provided in the eCRF.
The end-of-trial form will be completed when the subject has had their last visit.

11.9 Storage of biological samples

PK samples will be retained for as long as the quality of the material permits evaluation but for no longer than 12 months after completion of the clinical trial report (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

The trial is designed to evaluate the efficacy of tralokinumab in combination with TCS compared to placebo in combination with TCS in treating severe AD in subjects who are not adequately controlled with or have contraindications to oral CSA, a subgroup of AD patients that are difficult to treat because of the few approved treatment options available (35).

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 combined with TCS) are maintained and the possible observer bias regarding treatment effects is minimised.

By using a placebo-controlled parallel-group design for the treatment period, superiority of tralokinumab in combination with TCS versus placebo in combination with TCS can be investigated, hereby adding to the knowledge needed for positioning tralokinumab in the AD treatment pathway.

Stratification by prior CSA use (yes/no), country (Germany: yes/no), 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 included age range.

Among the key inclusion criteria for entry into the trial are a diagnosis of AD (as defined by the Hanifin and Rajka 1980 criteria for AD, see Appendix 4) at screening and a history of AD for at least one year, to ensure correct diagnosis and rule out differential diagnoses. A prerequisite for inclusion into the trial is also a documented history of treatment failure with CSA or not being a candidate for CSA.

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 (26).

- EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (27).
- SCORAD is a validated tool to assess the extent and severity of AD lesions and subjective symptoms (28).

The efficacy endpoints EASI75 and IGA score of 0 or 1 are recognised as important endpoints in clinical trials in AD by European regulators.

Several validated patient-reported questionnaires (SF-36, POEM, DLQI, EQ-5D-5L, and HADS) have been included to assess the efficacy of tralokinumab on PROs 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.

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

Safety will be assessed using standard clinical methods of subject evaluations, such as AE monitoring, vital signs, ECGs, 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 final visit in LP0162-1346 should be reported in LP0162-1346. 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 (i.e. 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 must be recorded whether 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 trial treatment: Any action taken with IMP or AxMP as a consequence of the AE must be recorded (dose not changed, dose reduced, dose increased, drug interrupted, drug withdrawn, not applicable, unknown).

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

13.4 Reporting of serious adverse events

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

13.4.1 Investigator reporting responsibilities

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

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

Global Safety at LEO

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

Fax number: +45 7226 3287

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

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

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

SAEs occurring after the completion of the clinical trial (i.e., after the last safety follow-up visit at Week 40) should not be routinely sought or collected. However, such events should be reported to Global Safety at LEO (see contact details above) if the investigator becomes aware of them.

13.4.2 LEO reporting responsibilities

Global Safety at LEO 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, current edition, must be used.
- For the AxMP (mometasone furoate, 0.1% cream), the latest version of the approved summary of product characteristics (SmPC) must be used.

Global Safety at LEO 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.

All SAEs which are assessed as causally related to the IMP **by either the investigator or LEO** (ICH E2A Guideline), and which are unexpected (Suspected, Unexpected Serious Adverse Reactions [SUSARs]), are subject to expedited reporting to regulatory authorities and 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.

13.5 Other events that require expedited reporting: pregnancy

Any pregnancy occurring during the clinical trial must be reported to LEO 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 (Section 10.2.1).

13.6 Reporting of other events

13.6.1 Adverse events of special interest

The events listed in Panel 11 are considered AEs of special interest (AESIs) in this trial and will require additional details to be recorded in the eCRF. LEO 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 11: Adverse events of special interest

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

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

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

13.6.2 Overdose

An overdose is defined as a subject receiving a 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).

LEO 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 a 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 cannot be expected to recover during the trial or the safety follow-up periods, for example chronic or stabilised conditions, 'not recovered' should be reported as a final outcome. 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.*" (36).

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 – 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 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

With a significance level of 5%, a sample size of 250 subjects will provide 99% power for detecting a treatment difference for the primary endpoint, assuming an EASI75 response rate at Week 16 of 40% vs 15% for tralokinumab+TCS and placebo+TCS, respectively. Assuming a response rate of 30% vs 15% in reduction of Worst Daily Pruritus NRS (weekly average) score of at least 4 from baseline to Week 16 for tralokinumab+TCS and placebo+TCS, respectively, the trial will provide at least 80% power for rejecting the hypotheses related to the primary endpoint and the secondary endpoint evaluating pruritus at Week 16.

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All subjects randomised to treatment and exposed to the IMP will be included in the full analysis set (FAS) and will be analysed for efficacy. Exclusions from the FAS can be considered in special cases as described in the ICH E9 guideline, Section 5.2.1 (37). If it is decided to exclude a randomised subject from the FAS, a justification addressing ICH E9 will be given.

The following safety analysis sets are applied:

- ‘safety analysis set’ for all subjects exposed to IMP within the treatment period.
- ‘safety follow-up analysis set’ for all subjects exposed to IMP within the safety follow-up period.

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

14.3 Statistical analysis

14.3.1 Aspects related to the COVID-19 pandemic

As the implications of the COVID-19 pandemic will, extraordinarily, influence trial events and data in manners not foreseen by the protocol, this section is introduced to elaborate on the COVID-19 pandemic related aspects that may require special handling depending on the original research question.

- **Permanent discontinuation of IMP due to the COVID-19 pandemic**:

  In general, permanent discontinuation of IMP can be interpreted as lack of efficacy of IMP and is therefore in some of the pre-specified analyses in the original protocol used to conclude non-response of the relevant subject. This interpretation is not appropriate when permanent discontinuation of IMP is caused by an external circumstance related to the COVID-19 pandemic.

  The causal relationship to the COVID-19 pandemic will be documented in the eCRF. The handling of permanent discontinuation of IMP will depend on whether it is due to the COVID-19 pandemic or not. The date of this event will be the date of permanent discontinuation of IMP.

- **Use of rescue treatment due to unavailability of IMP related to the COVID-19 pandemic**:

  Analogous to the handling of permanent discontinuation of IMP, interpretation of rescue treatment as lack of efficacy of IMP is not appropriate if rescue treatment is administered to compensate for unavailability of IMP due to the COVID-19 pandemic. It is therefore likewise relevant to determine whether this is the case.

  The collection of concomitant medication does not allow for directly linking rescue treatment to the COVID-19 pandemic. Instead, rescue treatment will be attributed to the COVID-19 pandemic if it is administered while IMP dosing is missing due to the COVID-19 pandemic or if it is given after permanent discontinuation of IMP due to the COVID-19 pandemic (these underlying conditions may both be fulfilled).

  Hence, rescue treatment will be attributed to the COVID-19 pandemic if it is administered in a time period where IMP is unavailable due to the COVID-19 pandemic. Such periods can be one of the following:

  1. From the date of a conducted scheduled visit without IMP dosing due to the COVID-19 pandemic until the date of the next administered dose.
  2. From 3 days prior to the planned date of a scheduled visit which is not conducted due to the COVID-19 pandemic until the date of the next administered dose.
  3. From the date of permanent discontinuation of IMP due to the COVID-19 pandemic.

  The date of this event will be the date of the administration of rescue treatment.

- **Prolonged interruption of IMP dosing due to the COVID-19 pandemic**:

  A temporary pause in dosing due to the COVID-19 pandemic may influence the interpretation of the subsequent outcome for the subject, and the event will therefore be reported.

  At the first occurrence, for which a subject misses IMP doses in one of the 4 following scenarios, the subject will be defined as having a prolonged interruption of IMP due to the COVID-19 pandemic:

  1. 3 consecutive missed IMP doses, for which at least one of them is due to the COVID-19 pandemic.
  2. 2 consecutive missed IMP doses, for which at least one of them is due to the COVID-19 pandemic and the third consecutive IMP dose is delayed for more than 7 days beyond the planned date of the IMP dosing.
  3. Week 22 and Week 24 IMP doses and the Week 26 visit are missed, for which at least one of them is due to the COVID-19 pandemic.
  4. Week 22 and Week 24 IMP doses are missed, for which at least one of them is due to the COVID-19 pandemic, and the Week 26 visit is delayed for more than 7 days beyond the planned date.

  In scenarios 1 and 3, the start date of the event will be the planned date of the third consecutive missed IMP dose or the Week 26 visit. In scenarios 2 and 4, the start date of the event will be the planned date of the third consecutive IMP dose +7 days or the Week 26 visit + 7 days.

- **Missing data due to the COVID-19 pandemic**:

  The collection of data at planned visits allows to report if data is missing due to the COVID-19 pandemic, either due to the subject being prohibited from vising the sites or the visit being performed via telephone/video, thereby only allowing for a subset of data to be collected.

  In the context of some of the efficacy analyses, data recorded missing due to the COVID-19 pandemic will be handled differently from data missing for other reasons. As an example, it may not be reasonable to impute missing binary responder values as a non-response if the missingness is due to the COVID-19 pandemic.

  It should be noted that a subject may have missing data due to the COVID-19 pandemic, even though the subject may not have discontinued IMP permanently or temporarily due

to the COVID-19 pandemic. This could e.g. be the case if the subject continue treatment with tralokinumab via home-use (Appendix 8).

- **Infection with COVID-19**:

  Infection with COVID-19 as an AE may give rise to one of the scenarios described above but will not be handled differently from other types of AEs.

14.3.2 Disposition of subjects

For all randomised subjects the reasons for permanent discontinuation of IMP and for withdrawal from the trial will be presented by treatment group.

Permanent discontinuation of IMP due to the COVID-19 pandemic will be added to the list of reasons and identified based on the information documented in the eCRF.

14.3.3 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects. The presentations will be overall and by treatment group. Demographics (age, sex, race, and ethnicity) and baseline disease characteristics (IGA, EASI, SCORAD, DLQI, and Worst Daily Pruritus NRS score) will be presented by the stratification factors: prior CSA use (yes/no), country (Germany: yes/no), and baseline disease severity (IGA 3 or 4).

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 medications, and previous AD treatments.

14.3.4 Exposure and treatment compliance

Exposure

Exposure to treatment will be presented for the safety analysis set as days of exposure per treatment group.

Treatment compliance

Compliance to treatment regimen will be recorded in the eCRF. If any complications or deviations in administration are observed, these will be described as protocol deviations. Treatment compliance will be presented for the total missed IMP doses, missed IMP doses not due to the COVID-19 pandemic, and the missed IMP doses due to the COVID-19 pandemic for the safety analysis set for each treatment group.

14.3.5 Rescue treatment

Rescue treatment will be defined by the following algorithm:

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

- ATC2 code H02
- Preferred name Methotrexate, Methotrexate sodium, Ciclosporin, Azathioprine, Mycophenolate-mofetil, Mychophenolate-acid, Mycophenolate-sodium, Dupilumab, Crisaborole, or Alitretinoin
- ATC4 code D07AD or D07BD or D07CD or D07XD
- Confirmed rescue treatment (by investigator) in reported term for the indication, and ATC4 code D07AB or D07BB or D07CB or D07XB or D07AC or D07BC or D07CC or D07XC

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

Rescue treatment will be summarised for the entire treatment period as well as for the period up until the Week 16 visit (actual or nominal). Rescue treatment will also be summarised for the periods prior to and after the start of the COVID-19 pandemic, within the treatment period. The start date(s) of the COVID-19 pandemic will be decided prior to unblinding in the statistical analysis plan, possibly reflecting on when trial procedures were disrupted on a national level.

Additionally, rescue treatment will be summarised for the entire treatment period by the variables: prior CSA use (yes/no), country (Germany: yes/no), and baseline disease severity (IGA 3 or 4).

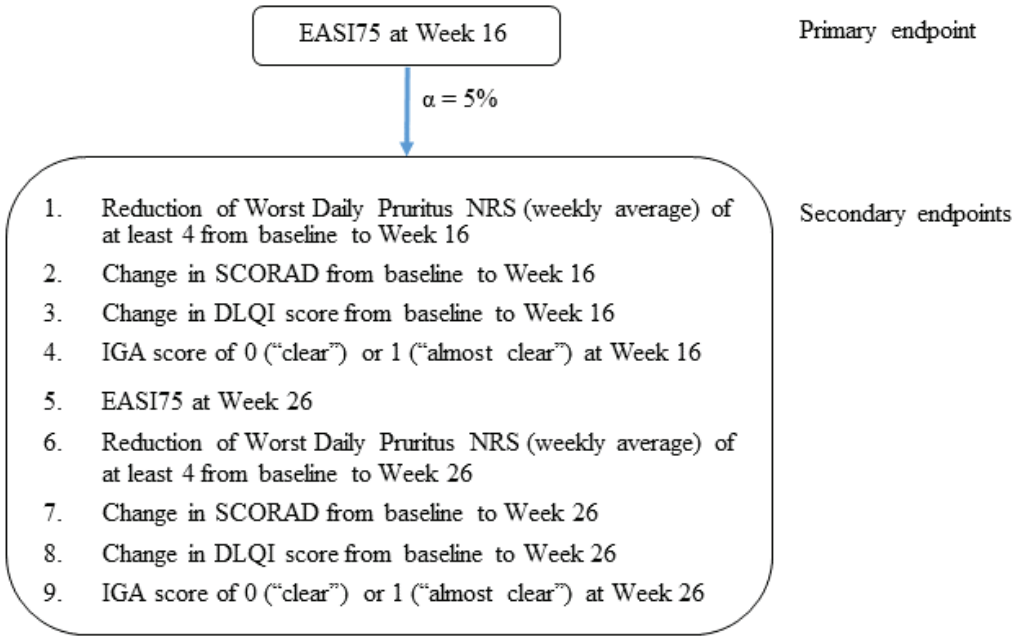
A summary table of rescue treatment by type (topical and systemic) and by overall group (corticosteroids, immunosuppressants, and other) will be made for the entire treatment period as well as for the period up until the Week 16 visit (actual or nominal).

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

14.3.6 Testing strategy

The primary and secondary endpoints will be evaluated hierarchically in the order shown in Panel 12. The hypothesis relating to a specific endpoint cannot be rejected unless all hypotheses relating to endpoints earlier in the hierarchy are also rejected at the 5% significance level. Hypothesis testing will be based on the primary analysis of the primary estimand for each associated endpoint.

Panel 12: Testing hierarchy for primary and secondary endpoints



Abbreviations: α = statistical significance level; DLQI = Dermatology Life Quality Index; EASI75 = at least 75% reduction in Eczema Area and Severity Index score; IGA = Investigator's Global Assessment; NRS = numeric rating scale; SCORAD = SCOring Atopic Dermatitis.

14.3.7 Intercurrent events

The applied estimands incorporate the following 3 main subject-specific intercurrent events that influence how the treatment effects are estimated.

- **Initiation of rescue treatment**:
  Some of the estimands use the initiation of rescue treatment 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 10.3. This can be at the subject's own initiative, at the investigator's discretion, or if the subject is 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 is used to modify an applied endpoint value.

- **Subject-onset of the COVID-19 pandemic**:
  This event is introduced to mitigate the external influence that the occurrence of the COVID-19 pandemic could have on the compliance of a subject with planned trial procedures and on the resulting interpretation of the trial.

  The event reflects the first occasion when the COVID-19 pandemic prevents a subject from complying with the protocol in a substantial manner. As described in Section 14.3.1, the circumstances arising from the COVID-19 pandemic might for example prevent a subject from receiving IMP or from conducting visits to the site, whereby planned assessments and procedures could become missing.

  For a given subject, this event is defined as the first occurrence of either of the 3 underlying COVID-19 pandemic-related scenarios defined in Section 14.3.1:

  - Permanent discontinuation of IMP due to the COVID-19 pandemic.
  - Use of rescue treatment due to unavailability of IMP related to the COVID-19 pandemic.
  - Prolonged interruption of IMP dosing due to the COVID-19 pandemic.

  As for the other 2 intercurrent events (initiation of rescue treatment and permanent discontinuation of IMP), collected and/or missing data following the start of the event will be handled differently from other data in especially the 'COVID-19 modified composite' estimand.

In addition to the above-mentioned 3 intercurrent events, the COVID-19 pandemic makes it appropriate to introduce an attribute of individual data points that influences their handling in some of the estimands:

- **Missing data due to the COVID-19 pandemic**:
  This attribute is related to a missing data point (assessment) that is accounted for in a given estimand analysis. It is assigned to each data point that is missing due to the COVID-19 pandemic as outlined in section 14.3.1.

An overview of how the applied estimands handle the intercurrent events and missing data is presented below (Panel 13).

Panel 13: Handling of intercurrent events and missing data in the primary analysis of estimands

		Binary endpoints				Continuous endpoints		
First prior intercurrent event	**Missing or observed data**	**COVID-19 modified composite**	**Composite**	**treatment policy**	**hypothetical**	**hypothetical**	**treatment policy**	**COVID-19 modified composite**
Rescue treatment	**Missing data**	Non-response	Non-response	Event ignored[1]	MI	Not used	Event ignored[1]	WOCF
	Observed data	Non-response	Non-response	Event ignored[1]	MI	Not used	Event ignored[1]	WOCF
Permanent discontinuation of IMP	**Missing data**	Non-response	Non-response	MI – discontinued	MI	Not used	MI – discontinued	WOCF
	Observed data	Non-response	Non-response	Used	MI	Not used	Used	WOCF
Subject-onset of the COVID-19 pandemic	**Missing data**	MI	Event ignored[2]	MI – not discontinued	MI	Not used	MI – not discontinued	MI
	Observed data	MI	Event ignored[2]	MI – not discontinued	MI	Not used	MI – not discontinued	MI
No prior intercurrent event	**Missing data not due to the COVID-19 pandemic**	Non-response	Non-response	MI – not discontinued	MI	Not used	MI – not discontinued	MI
	Missing data due to the COVID-19 pandemic	MI	Non-response	MI – not discontinued	MI	Not used	MI – not discontinued	MI
	Observed data	Used	Used	Used	Used	Used	Used	Used

Abbreviations: COVID-19 = Coronavirus Disease 2019; IMP = investigational medicinal product; MI = multiple imputation; MI – discontinued = MI method using only retrieved data at Week 16 / Week 26 from discontinued subjects; MI – not discontinued = stepwise MI method using data from not discontinued subjects.; WOCF = Worst observation carried forward.

1) Rescue treatment is ignored as an intercurrent event in the treatment policy estimands.

2) Subject-onset of the COVID-19 pandemic is ignored as an intercurrent event in the composite estimand.

14.3.8 Analysis of primary efficacy endpoint

4 estimands addressing different aspects of the trial objectives will be defined for the primary efficacy endpoint (Panel 13):

- Primary estimand: 'COVID-19 modified composite'
- Secondary estimand: 'composite'
- Tertiary estimand: 'treatment policy'
- Quaternary estimand: 'hypothetical'

All analyses will be based on the FAS.

14.3.8.1 Primary estimand: 'COVID-19 modified composite'

The primary estimand for the primary endpoint will be:

- Treatment difference in response rates of EASI75 after 16 weeks achieved without rescue treatment and treatment discontinuation, as if the COVID-19 pandemic did not happen

The primary estimand assesses the expected difference in response rates (defined as response obtained without initiation of any rescue treatment and/or permanent discontinuation of IMP) after 16 weeks, resulting from initiation of a treatment regimen with tralokinumab+TCS compared to a treatment regimen with placebo+TCS.

Primary analysis for the primary estimand

Subjects who prior to the Week 16 visit have received rescue treatment or permanently discontinued IMP, without subject-onset of the COVID-19 pandemic, will be considered non-responders at all visits after the relevant event occurs (Panel 13).

The non-responder imputation reflects an assumption that such initiation of rescue treatment and permanent discontinuation of IMP indicates failure of the randomised treatment to achieve response. Furthermore, this reflects that a (possible) observed positive response after initiation of rescue treatment or permanent discontinuation of IMP is not attributable to the randomised treatment.

Any missing or collected data from subjects who have subject-onset of the COVID-19 pandemic as their first prior intercurrent event will not be used, but instead imputed assuming missing at random (MAR) following the start of subject-onset of the COVID-19 pandemic.

Data missing prior to any intercurrent event will be handled as non-response, unless data is missing due to the COVID-19 pandemic, in which case it will be imputed assuming MAR.

The procedure for imputing values according to the rules described will be implemented in a 2-step procedure, where all missing or ignored data (irrespectively of reason) initially will be imputed using MAR based on available data from all subjects. The non-responder imputation of data not affected by the COVID-19 pandemic will be handled subsequently.

The initial MAR imputation will be implemented using the same multiple stepwise imputation method as specified in Section 14.3.8.4 for the primary analysis of the hypothetical binary estimand. The multiple imputation (MI) procedure sequentially builds 100 complete data sets by stepwise use of an ANCOVA model from Week 2 to Week 16 assuming MAR within treatment groups.

When building the 100 complete data sets, available data from all subjects will be used, excluding individual subject data captured after initiation of rescue treatment, permanent discontinuation of IMP, or subject-onset of the COVID-19 pandemic.

Once the 100 complete data sets have been generated by MI, non-responder imputation of relevant data points not affected by the COVID-19 pandemic will be applied according to the rules described above.

For each of the resulting 100 complete data sets, the difference in response rates between treatment groups will be analysed using the Mantel-Haenszel risk difference stratified by prior CSA use (yes/no) and baseline disease severity (IGA 3 or 4). The estimates and standard errors from the 100 analyses will be pooled to one estimated treatment difference and associated standard error using Rubin's rule to draw inference. From these pooled estimates, the 95% CI for the treatment difference will be calculated.

Sensitivity analysis for the primary estimand

A tipping-point analysis will be performed with the purpose of assessing the robustness of results of the primary analysis (for the primary estimand) with respect to the MAR assumption for missing data due to the COVID-19 pandemic.

The tipping-point analysis will only test the MAR assumption among subjects in the tralokinumab+TCS group who had missing data imputed at the Week 16 visit due to subject-onset of the COVID-19 pandemic or data missing due to the COVID-19 pandemic. The tipping-point analysis will assess how severe the departure from the MAR assumption in the tralokinumab+TCS group has to be in order to impact the results (i.e. to change the

conclusion of the primary analysis of the primary estimand) from significant to non-significant.

The tipping-point analysis will be performed using the MAR imputed Week 16 data from the primary analysis of the estimand. For each of the 100 imputed datasets, a quantity Δ will be added to all imputed Week 16 values for subjects in the tralokinumab+TCS group who have had subject-onset of the COVID-19 pandemic prior to Week 16 or have data missing due to the COVID-19 pandemic at Week 16, thereby causing the imputed values to be 'shifted' by Δ (Δ = 0 implies MAR).

Δ will be defined from the min to the max of the analysed score (i.e. EASI). Each of the 100 modified imputed datasets will then be analysed in the same way as for the primary analysis for the primary estimand. The tipping-point is then found as the value of Δ which changes the conclusion (of the primary analysis) from significant to non-significant. Tipping-points will be judged from a clinical point of view.

The analysis will use the same method as the primary analysis of the primary estimand.

14.3.8.2 Secondary estimand: 'composite'

The secondary estimand for the primary endpoint will be:

- Treatment difference in response rates of EASI75 after 16 weeks achieved without either rescue treatment or treatment discontinuation, as if the COVID-19 pandemic did not happen

The secondary estimand assesses the expected difference in response rates (defined as response obtained without initiation of any rescue treatment or permanent discontinuation of IMP) after 16 weeks, resulting from initiation of a treatment regimen with tralokinumab+TCS compared to a treatment regimen with placebo+TCS. Essentially, this estimand will not take into account whether or not rescue treatment or permanent discontinuation of IMP occur due to the COVID-19 pandemic, and any subject-onset of the COVID-19 pandemic will be ignored in the analysis.

Primary analysis for the secondary estimand

Subjects who prior to the Week 16 visit have received rescue treatment or permanently discontinued IMP will be considered non-responders, reflecting an assumption that initiation of rescue treatment or permanently discontinued IMP indicates failure of the randomised treatment to achieve response. It is also assumed that a (possible) observed positive response after initiation of rescue treatment or permanently discontinued IMP is not attributable to the

randomised treatment. Missing data for subjects who do not attend the Week 16 visit and where rescue treatment or permanently discontinued IMP has not been used prior to Week 16, will be imputed as non-responders (Panel 13).

The difference in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test stratified by prior CSA use (yes/no) and baseline disease severity (IGA 3 or 4). The treatment estimate and the corresponding 95% CI will be presented.

Sensitivity analyses for the secondary estimand

The purpose of the sensitivity analysis is to assess the robustness of results of the primary analysis for the secondary estimand with respect to the assumption regarding any missing Week 16 data, among subjects who did not use any rescue treatment or permanently discontinued IMP.

A tipping-point analysis using MI will be performed. The procedure will be as follows: subjects in the tralokinumab +TCS group with missing Week 16 data will per default be considered non-responders, while missing Week 16 data for subjects in the placebo+TCS group who did not use rescue treatment or permanently discontinued IMP will be imputed from a Bernoulli distribution with parameter p (ranging from 0 to 1). By varying the parameter p, different percentages of subjects in the placebo+TCS group will be assumed to be responders (deviating from the default 0% of the primary analysis of the secondary estimand). The tipping-point is then found as the value of p which changes the conclusion of the primary analysis from significant to non-significant. Tipping-points will be judged from a clinical point of view.

The MI procedure will include the following steps for each value of p:

- 100 copies of the dataset will be generated (seed=11109946) and missing Week 16 data will be imputed for subjects in the placebo+TCS group from a Bernoulli distribution with parameter p.
- For each of the 100 complete data sets, the difference in response rates will be analysed as specified for the primary estimand.

14.3.8.3 Tertiary estimand: ‘treatment policy’

The tertiary estimand for the primary endpoint will be:

- Treatment difference in response rate of EASI75 after 16 weeks between tralokinumab+TCS and placebo+TCS regardless of rescue treatment and IMP discontinuation, as if the COVID-19 pandemic did not happen

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

Primary analysis for the tertiary estimand

Data retrieved at Week 16 for subjects who prior to Week 16 have permanently discontinued IMP for other reasons than the COVID-19 pandemic will be included in the analysis.

For subjects who have subject-onset of the COVID-19 pandemic prior to Week 16 and prior to any permanent discontinuation of IMP not due to the COVID-19 pandemic, any observed data from these subjects will be ignored and treated as missing in the same manner as missing data from not discontinued subjects in the analysis (Panel 13).

Imputation of missing data at Week 16 will be done using multiple imputations within 4 groups defined according to randomised treatment group and whether or not subjects have permanently discontinued IMP prior to Week 16. Within a given treatment group, 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/treated as missing.

For not discontinued subjects, the stepwise multiple imputations procedure will be conducted in the same way, using the same seeds, as specified for the primary analysis of the quaternary 'hypothetical' estimand described in Section 14.3.8.4.

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, a separate imputation model at Week 16 with only prior CSA use (yes/no) and baseline disease effects (IGA as a factor and EASI as a covariate) will be applied for discontinued subjects. Some factors may have to be omitted, depending on the observed data, e.g. if all subjects have the same baseline disease severity. In that case the preferred order of elimination of the effects from the imputation model will be: prior CSA use and baseline disease effects (seed=12576546).

The imputed datasets will be analysed in the same way as specified for the primary analysis of the quaternary 'hypothetical' estimand in Section 14.3.8.4.

Sensitivity analyses for the tertiary estimand

Rather than imputing Week 16 data as described in the primary analysis of the tertiary estimand, missing observations not caused by subject-onset of the COVID-19 pandemic or not missing due to the COVID-19 pandemic, 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. Missing observations due to either subject-onset of the COVID-19 pandemic or missing due to the COVID-19 pandemic, will be imputed as described in the primary analysis of the tertiary estimand.

In case the number of discontinued subjects attending the nominal Week 16 visit is too low to fit the imputation model in the primary analysis of the tertiary estimand, the sensitivity analysis will become the primary analysis of the tertiary 'treatment policy' estimand.

14.3.8.4 Quaternary estimand: 'hypothetical'

The quaternary estimand for the primary endpoint will be:

- Treatment difference in response rates of EASI75 after 16 weeks if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently, no rescue treatment was made available, and as if the COVID-19 pandemic did not happen before Week 16.

The quaternary estimand assesses the expected difference in response rates achieved when adhering to the treatment regimen tralokinumab+TCS with no rescue treatment or subject-onset of the COVID-19 pandemic as compared to a treatment regimen with placebo+TCS with no rescue treatment or subject-onset of the COVID-19 pandemic.

Primary analysis of the quaternary estimand

Data collected after permanent discontinuation of IMP, after initiation of rescue treatment, or after subject-onset of the COVID-19 pandemic will not be applied in the analysis (Panel 13).

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 2 groups defined according to randomised treatment group assuming that data is MAR within each group.

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=12456746).
2. For each of the 100 copies of the dataset, an analysis of covariance (ANCOVA) model is fitted to the EASI value at Week 2. The model will include effects of baseline EASI as a covariate, and prior CSA use (yes/no), 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 (seed=12576546).
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 prior CSA use, country, 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 the remaining visits starting with Week 6 until Week 16. The only modification is that the EASI values from the preceding 2 visits will be included as covariates in addition to baseline EASI, and prior CSA use 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 between treatment groups will be analysed using the Mantel-Haenszel risk difference stratified by prior CSA use (yes/no) and baseline disease severity (IGA 3 or 4). The estimates and standard errors from the 100 analyses will be pooled to one estimated treatment difference and associated standard error using Rubin's rule to draw inference. From these pooled estimates, the 95% CI for the treatment difference will be calculated.

Sensitivity analysis for the quaternary estimand

Rather than assuming that observations are MAR within each treatment group, it is assumed that missing data from subjects who had any of the intercurrent events in the tralokinumab+TCS group will resemble missing data from subjects from the placebo+TCS group who had none of the intercurrent events. The underlying assumption is that the effect of tralokinumab following rescue treatment, permanent treatment discontinuation, or subject-onset of the COVID-19 pandemic is similar to the effect of placebo. It should be noticed that

this assumption is pronouncedly conservative in favour of placebo as it tends to minimise the differences between treatment groups.

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

14.3.9 Analysis of secondary endpoints

The secondary endpoints evaluate the impact of 16 and 26 weeks of treatment on (i) itch, (ii) severity and extent of AD, and (iii) HRQoL. The corresponding endpoints are (i) reduction (yes/no) of Worst Daily Pruritus NRS average score for the past week (hereinafter 'Worst Daily Pruritus NRS weekly average') of at least 4 from baseline to Week 16/ Week 26, (ii) the change from baseline to Week 16/ Week 26 in SCORAD, the (iii) change from baseline to Week 16/ Week 26 in DLQI score, (ii) IGA score of 0 (clear) or 1 (almost clear) at Week 16/ Week 26, (ii) EASI75 at Week 26. Worst Daily Pruritus NRS over the last week prior to baseline (Day -6 to 0) will be used to calculate the baseline itch (see also inclusion criterion no. 9).

EASI75 at Week 26 is a binary endpoint and it will be analysed as described for the primary endpoint (EASI75 at Week 16) using all 4 estimands with the modification that the imputation algorithm will be applied until Week 26.

Reduction of Worst Daily Pruritus NRS weekly average of at least 4 from baseline to Week 16/ Week 26 is a binary endpoint, and it will be analysed as described for the primary endpoint (EASI75 at Week 16) using all 4 estimands with the modification of the ANCOVA imputation model that reduction of Worst Daily Pruritus NRS weekly average replaces EASI where preceding values are used as covariates. Only subjects with an average Worst Daily Pruritus NRS score of 4 or above at baseline will be included in these analyses.

For each of the binary secondary endpoints, tipping-point analyses using the method described for the tipping-point analyses of the binary primary endpoint (EASI75 at Week 16) will be added as sensitivity analyses for the primary estimand.

Subgroup analysis of binary endpoints

Subgroup analyses will be applied for the primary analyses of the primary and tertiary estimands for the groups: sex, prior CSA use (yes/no), baseline disease severity (IGA 3 or 4),

country (Germany: yes/no), and baseline age (≤65 years, >65 years). Interaction between subgroups and treatment effect will be tested using a conditional logistic regression. The conditional logistic regression model will implement a test of the treatment-by-subgroup interaction while adjusting for the same strata used in the corresponding analyses. The model used for the test of interaction will be:

$$Y = \text{treatment} + \text{subgroup} + \text{treatment*subgroup}$$

The stratification variables used will be the same as the ones used in the corresponding analyses and will be specified as strata to the conditional logistic regression model. If a stratification variable (prior CSA use [yes/no] or baseline disease severity [IGA 3 or 4]) is the subject of a subgroup analysis, then the variable will be omitted from the stratification for that analysis. The p-value of the interaction term between treatment and the subgroup will be reported as the interaction test outcome. Subgroup analyses will be performed for the following endpoints:

- EASI75 at Week 16
- EASI75 at Week 26
- Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to Week 16.
- Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to Week 26
- IGA score of 0 or 1 at Week 16
- IGA score of 0 or 1 at Week 26

The binary endpoint IGA 0/1 will be analysed as described for the primary endpoint using all 4 estimands with the modification that the following imputation algorithm will be used for the primary, tertiary, and quaternary estimands.

IGA 0/1 responder imputation

Imputation of missing binary IGA 0/1 data at Week 16 and Week 26 will be done using multiple imputations of the underlying 5-point IGA values within the 2 groups defined according to randomised treatment group assuming that data is MAR within each group.

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 prior CSA use (yes/no) 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=37649846).
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 prior CSA use, 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 the remaining visits starting with Week 6 until Week 16 (or until Week 26 for the Week 26 endpoint) with the modification that only the IGA values from the 2 preceding visits will be included as factors in addition to prior CSA use, and baseline disease severity. The missing binary IGA 0/1 response at Week 16/ Week 26 will be derived from the corresponding underlying imputed IGA value.

The changes from baseline to Week 16/ Week 26 in SCORAD and DLQI scores, respectively, are continuous endpoints and will be analysed using 3 estimands addressing different aspects of the trial objectives (Panel 13):

- Primary estimand: ‘hypothetical’
- Secondary estimand: ‘treatment policy’
- Tertiary estimand: ‘COVID-19 modified composite’

All analyses will be based on the FAS.

14.3.9.1 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/ Week 26 in SCORAD and DLQI scores, respectively, if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently, no rescue treatment was made available, and as if the COVID-19 pandemic did not happen before Week 16/ Week 26.

The primary estimand assesses the expected benefit when adhering to the treatment regimen tralokinumab+TCS with no rescue treatment or subject-onset of the COVID-19 pandemic as compared to a treatment regimen with placebo+TCS with no rescue treatment or subject-onset of the COVID-19 pandemic.

Primary analysis of the primary estimand (continuous secondary endpoints)

Data collected after permanent discontinuation of IMP, after initiation of rescue treatment, or after subject-onset of the COVID-19 pandemic will not be included in the analysis (Panel 13).

The endpoints will be analysed using a repeated measurements model on the post-baseline responses up to Week 26 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 + prior CSA use + country + baseline IGA

This model assumes that data is MAR within each treatment group. The estimates will be presented with nominal p-values and 95% CI at each visit. The comparisons between tralokinumab+TCS and placebo+TCS will be at Week 16 and Week 26.

Sensitivity analysis for the primary estimand (continuous secondary endpoints)

Rather than assuming that observations are MAR within each treatment group it is assumed that missing data from subjects who had any of the intercurrent events in the tralokinumab+TCS group will resemble data from subjects from the placebo+TCS group who had none of the intercurrent events. Imputation of missing data at Week 16/ Week26 will be done using a pattern mixture model where missing data in the tralokinumab+TCS group as well as the placebo+TCS group will be imputed from the placebo+TCS group (using a so-called copy-reference approach). The procedure for the change from baseline in SCORAD at Week 16/ Week 26 is described below. The same procedure will be applied for the DLQI endpoint.

1. Intermittent missing values will be imputed in each group using a Markov Chain Monte Carlo method to obtain a monotone missing data pattern, and 100 copies of the dataset will be generated (seed=14563746).
2. For each of the 100 copies of the dataset, an ANCOVA model will be fitted to the SCORAD value at Week 2 in the placebo+TCS group. The model will include effects of baseline SCORAD as a covariate with prior CSA use (yes/no), country

(Germany: yes/no), 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+TCS group as well as the tralokinumab+TCS group (seed=65749346).

3. For each of the 100 copies of the dataset, missing values at Week 4 will be imputed in the same way as for Week 2. The imputations will be based on a similar ANCOVA model, but with SCORAD value at Week 2 included as an additional covariate. The parameters from the model will be estimated based on data from the placebo+TCS group. The estimated parameters, and their variances, will be used to impute missing values at Week 4 for both treatment groups.
4. This stepwise procedure will then be repeated sequentially for the remaining visits starting with Week 6 until Week 16 (or Week 26 for the Week 26 endpoint) with the SCORAD values from the preceding 2 visits included as covariates in addition to baseline SCORAD as a covariate, prior CSA use, country, and baseline disease severity as factors.

For each of the 100 imputed dataset, the change from baseline in SCORAD at Week 16/ Week 26 will be analysed using an ANCOVA model with effects of treatment, prior CSA use, country, baseline disease severity, and baseline SCORAD value as factors. The estimated difference at Week 16/ Week 26 will be derived together with the associated standard error. The estimates and standard errors from the 100 analyses are pooled to one estimate and associated standard error using Rubin's rule to draw inference. From these pooled estimates, the 95% CI for the treatment difference will be calculated.

14.3.9.2 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/ Week 26 in SCORAD and DLQI scores, respectively, between tralokinumab+TCS and placebo+TCS regardless of rescue treatment use and treatment discontinuation, as if the COVID-19 pandemic did not happen.

The secondary estimand assesses the average difference in change from baseline in SCORAD and DLQI at Week 16/ Week 26, resulting from initiation of a treatment regimen with tralokinumab+TCS and rescue treatment as compared to a treatment regimen with placebo+TCS and rescue treatment.

Primary analyses for the secondary estimand (continuous secondary endpoints)

Data retrieved at Week 16/ Week 26 for subjects who prior to Week 16/Week 26 have permanently discontinued IMP for other reasons than the COVID-19 pandemic will be included in the analysis.

For subjects who have subject-onset of the COVID-19 pandemic prior to Week 16/ Week 26 and prior to any permanent discontinuation of IMP not due to the COVID-19 pandemic, any observed data from these subjects will be ignored and treated as missing in the same manner as missing data from not discontinued subjects in the analysis (Panel 13).

Missing Week 16/ Week 26 data will be imputed using multiple imputations assuming that data is MAR within the groups used for imputation.

Imputation of missing data at Week 16/ Week 26 will be done using multiple imputations within 4 groups defined according to randomised treatment group and whether or not subjects have discontinued treatment prior to Week 16/ Week 26. Within a given treatment group, 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/ Week 26 value is missing/treated as missing.

For not discontinued subjects, the stepwise multiple imputations procedure will be conducted in the same way, using the same seeds, as specified for the imputation of the underlying EASI values in the primary analysis of the quaternary estimand for the binary endpoints (see Section 14.3.8.4).

For discontinued subjects, it is expected that the number of subjects with retrieved data at Week 16/ Week 26 will be too small to facilitate the same imputation model as mentioned just above. Consequently, an imputation model with prior CSA use (yes/no), country (Germany: yes/no), and baseline disease severity (IGA 3 or 4) as factors and baseline SCORAD/DLQI as a covariate will be applied for discontinued subjects. Some factors may have to be omitted, depending on the observed data, e.g. all subjects have the same baseline disease severity. In that case, the preferred order of elimination of the effects from the imputation model will be: country, prior CSA use, baseline disease severity, and baseline SCORAD/DLQI (seed=12576546).

Each of the 100 imputed datasets will be analysed as described in the sensitivity analyses for the primary estimand for the continuous secondary endpoints (see Section 14.3.9.1).

Sensitivity analyses for the secondary estimand (continuous secondary endpoints)

Rather than assuming that observations are MAR, it is assumed that missing data from subjects in the tralokinumab+TCS group who have/have not discontinued treatment prior to Week 16/ Week 26 will resemble data from subjects from the placebo+TCS group who have/have not discontinued treatment prior to Week 16/ Week 26.

Imputation of missing data at Week 16/ Week 26 will be done using a pattern mixture model where missing data in the tralokinumab+TCS group as well as the placebo+TCS group will be imputed from the placebo+TCS group (copy-reference approach). With this exemption, the MI 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 (Section 14.3.9.2).

14.3.9.3 Tertiary estimand for the continuous secondary endpoints: 'COVID-19 modified composite'

The primary estimand for the continuous tertiary endpoint will be:

- Treatment difference in change from baseline to Week 16/Week 26 in SCORAD and DLQI scores, respectively, without rescue treatment and treatment discontinuation, as if the COVID-19 pandemic did not happen

The continuous tertiary estimand assesses the expected treatment difference (obtained without initiation of any rescue treatment and/or permanent discontinuation of IMP) after 16/ 26 weeks, resulting from initiation of a treatment regimen with tralokinumab+TCS compared to a treatment regimen with placebo+TCS.

Primary analysis for the tertiary estimand (continuous secondary endpoints)

Data retrieved at Week 16/ Week 26, depending on the endpoint, for subjects who have received rescue treatment or permanently discontinued IMP prior to the visit, without subject-onset of the COVID-19 pandemic, will be considered non-responders by using worst observation carried forward (including the baseline value) (Panel 13).

Any missing or collected data from subject who have subject-onset of the COVID-19 pandemic as their first prior intercurrent event will not be used, but instead be imputed assuming MAR following the start of subject-onset of the COVID-19 pandemic.

Any data missing at the relevant visit from subjects without prior rescue treatment, permanent discontinuation of IMP, or subject-onset of the COVID-19 pandemic will be imputed assuming MAR.

The procedure for imputing values according to the rules described above will follow the same imputation procedure described in the primary analysis of the binary primary estimand. However, any data missing at the relevant visit from subjects without a prior intercurrent event will not be imputed as a 'non-responder' after the imputation step, but will be imputed assuming MAR.

For each of the resulting 100 imputed datasets, this primary analysis will be analysed using an ANCOVA model with effects of treatment, prior CSA use (yes/no), country (Germany: yes/no) and baseline disease severity (IGA 3 or 4) as factors. The estimates and standard errors from the 100 analyses are pooled to one estimate and associated standard error using Rubin's rule to draw inference. From these pooled estimates, the 95% CI for the treatment difference will be calculated.

14.3.9.4 Subgroup analysis of continuous endpoints

Subgroup analyses will be performed for the SCORAD and DLQI endpoints at Week 16 and Week 26 for the following groups: sex, prior CSA use, baseline disease severity (IGA 3 or 4), country, age (≤65 years, >65 years) for the primary analysis of primary and secondary estimands. For the primary estimand the following repeated measurements model with an unstructured covariance matrix and Kenward-Roger approximation of degrees of freedom will be applied (presented for subgroup sex).

Change from baseline in SCORAD

= sex × treatment × visit + baseline SCORAD × visit + CSA use +country + baseline IGA.

The interaction between sex and treatment effect will be tested at Week 16 and Week 26.

14.3.10 Analysis of other endpoints

All binary endpoints listed under 'Other endpoints' (Panel 4) will be analysed as for the primary analysis of the primary and secondary estimands for the primary endpoint and presented for the FAS at Week 16 and Week 26.

All continuous endpoints listed under 'Other endpoints' (Panel 4) will be analysed as for the primary analysis of the primary and secondary estimands for 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. For the Worst Daily Pruritus NRS and Eczema-related Sleep NRS scores, it is expected that subjects will return their eDiaries upon permanent discontinuation of IMP, and no data is available after that point. Thus, analysis

using the primary analysis of the secondary continuous estimand will not be possible in the 'Other endpoints' with Worst Daily Pruritus NRS or Eczema-related Sleep NRS scores.

To evaluate the efficacy related to health care resource utilisation, the amount of TCS used (assessed as the amount of TCS used between visits) will be determined over 2-week periods, and the number of days without topical treatment use (collected as Patient Days of Topical Treatment Use in the eDiary) will be determined over 1-week periods. The amount of TCS used and the number of days without topical treatment use will each be analysed using a repeated measurements model with an unstructured covariance matrix and the mean modelled as follows:

Y = treatment × [visit/week] + prior CSA use + country + baseline IGA

where 'Y' is either the amount of TCS used or the number of days without topical treatment use. Data obtained after permanent discontinuation of IMP, after initiation of rescue treatment, or after subject-onset of the COVID-19 pandemic will be excluded from the analyses.

14.3.11 Analysis of exploratory supporting endpoints

There will be performed longitudinal analyses by visit/week of all primary, secondary and 'Other' efficacy endpoints, as specified in Panel 4.

For the binary endpoints, the analyses will use the primary analysis of the primary estimand for each scheduled visit/week in the treatment period where an assessment is planned according to Panel 2. The variables used for stratification (prior CSA use [yes/no] and baseline disease severity [IGA 3 or 4]) will be the same as the ones used for the primary analysis of the primary estimand.

For the continuous endpoints, a repeated measurements model using the same method described in the primary analysis of the primary estimand of the continuous secondary endpoints. The estimates and differences will be presented with 95% CIs, and nominal p-values for each scheduled visit/week in the treatment period where an assessment is planned according to Panel 2.

14.3.12 Analysis of patient-reported outcomes

The PROs (POEM, DLQI, EQ-5D-5L [index and VAS scores], SF-36, and HADS) will be summarised by treatment group and visit using descriptive statistics based on the FAS.

The PROs collected in the eDiaries on a daily basis (Worst Daily Pruritus NRS, Eczema-related Sleep NRS) will all be summarised over time by treatment group using descriptive statistics based on the FAS.

To investigate a possible early onset of itch relief, a reduction in Worst Daily Pruritus NRS weekly average of at least 4 from baseline to Week 2 will be summarised by treatment group and analysed as described for the primary analysis of the primary estimand for the primary endpoint.

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 Weeks 16 and 26 will be summarised by treatment group and analysed as described for the primary analysis of the primary estimand for the primary endpoint.

The change from baseline to Weeks 16 and 26 in Eczema-related Sleep NRS weekly average, HADS, POEM, SF-36, and the EQ-5D-5L scores will be summarised by treatment group and domain, where applicable.

14.3.13 Analysis of safety

The analyses of safety will be based on the safety analysis set and the safety follow-up analysis set.

14.3.13.1 Adverse events

To assess the safety of tralokinumab in combination with TCS when used to treat severe AD for 26 weeks, the frequency of AEs and SAEs are included as additional secondary endpoints.

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 (PTs) and primary system organ class (SOC).

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

An overall summary of treatment-emergent AEs (the number of AEs, the number and percentage of subjects with an AE, and the event rate of AEs), deaths, SAEs, permanent 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 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 and AxMP (TCS) for each type of AE will be tabulated by treatment group.

Related AEs are defined as AEs for which the investigator has not described the causal relationship to 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 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 or permanent discontinuation of IMP will be tabulated and listed.

Due to the COVID-19 pandemic and the implementation of home-use (self-injection) with telephone/video follow-up, overall safety monitoring could be impacted. To assess this, all AEs collected prior to and after the start of the COVID-19 pandemic will, in addition to being presented together, be presented separately for the overall summary of AEs and for all the AEs by SOC and PT.

14.3.13.2 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, 1st quartile, 3rd quartile, minimum, and maximum values for the safety analysis set. Vital signs will be listed for the safety follow-up analysis set.

14.3.13.3 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, 1st quartile, 3rd

quartile, minimum, and maximum values for the safety analysis set. Laboratory parameters will be listed for the safety follow-up 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.

14.3.13.4 Anti-drug antibodies

The frequency of ADA is a secondary endpoint included to assess the safety and tolerability (immunogenicity) of tralokinumab in combination with TCS.

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

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

The ADA status will be categorised as follows:

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

- No post-baseline ADA assessment.

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

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

14.3.14 Pharmacokinetics

All the PK samples in the trial are trough samples. The trough concentration (C_{trough}) will be listed by treatment group and descriptive statistics will be applied. C_{trough} values from subjects with positive ADA/nAB will be compared to values from subjects with negative ADA/nAB if data permits.

14.3.15 Interim analysis

No interim analysis is planned.

14.3.16 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, 1st quartile, 3rd quartile, 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 and the analysis set definition document 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, and/or in the CTR dependent on the type of deviation.

14.3.17 Handling of missing values

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

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Appendix 1: Definitions of adverse events and serious adverse events

Adverse event definition

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

AEs 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.

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

Outcome

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

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

Note that as per the above definition, LEO 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 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 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 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 '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.

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 (38) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (39).
- Current version of applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines (40).
- EU's General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

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

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

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

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

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the local IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- 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 will receive written and verbal information concerning the clinical trial. This information will emphasise that participation in the clinical trial is voluntary and that the subject may withdraw from the clinical trial at any time and for any reason. All subjects will be given an opportunity to ask questions and will be given sufficient time to consider before consenting.

The subject's signed and dated informed consent to participate in the clinical trial will 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.

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

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 and shall not be used by the investigator for purposes other than this clinical trial.

The investigator agrees that LEO 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 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 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 and third parties acting on behalf of LEO.

Processing of personal data on behalf of LEO requires a written agreement between LEO 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 must ensure that collection, processing and transfer of personal data are in compliance with applicable legislation on data protection and privacy, including but not limited to the EU General Data Privacy Regulation.

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

LEO 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 groups of tralokinumab+TCS or placebo+TCS for 26 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 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 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 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 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, 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 or designee electronically (e.g. laboratory data). The investigator or staff authorised by the investigator will enter subject data into electronic CRFs (eCRFs). Data recorded in the eCRFs will be accessible to the trial site and LEO personnel immediately after entry. The eCRFs must be maintained in an up-to-date state by the trial site at all times.

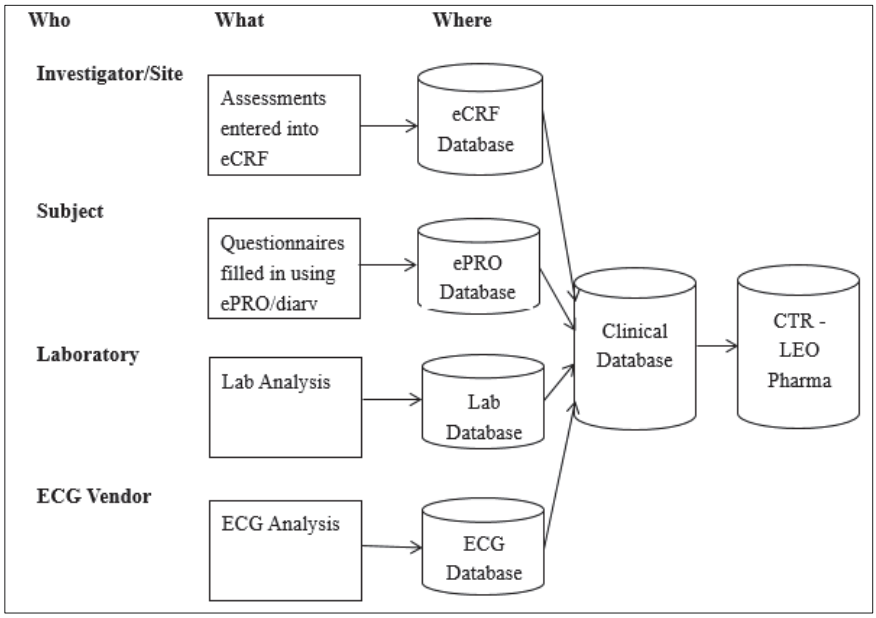
The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRFs used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original 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 electronic 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 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 14.

Panel 14: 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 (40). Essential trial documents must be stored until LEO 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 in accordance with LEO's Position on Public Access to Clinical Trial Information no later than 12 months after trial completion. Trial results may also become reported in www.ClinicalTrials.gov, www.clinicaltrialsregister.eu and national data registries in accordance with applicable law and regulations after clinical trial completion or premature termination. LEO may also

provide researchers access to anonymised patient level data for further research. Publication and access will be in accordance with LEO's Position on Public Access to Clinical Trials which can be found on LEO'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 a copy of all such manuscripts and/or presentations. LEO shall have rights to review and comment. The investigator shall consider LEO'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 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 withhold the publication or presentation to allow LEO 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, LEO 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 complies with GPP3 standards and the recommendations from the International Committee of Medical Journal Editors. LEO 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 also follows the CONSORT reporting guidelines (22).

Appendix 3F: Insurance

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

Appendix 3H: Trial and site closure

Premature termination of trial or trial site

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

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

Appendix 3I: Responsibilities

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

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

Source: Hanifin and Rajka, 1980 (21)

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

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

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

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

Appendix 5: Guidance for anaphylaxis diagnosis

Source: Sampson et al., 2006 (41)

The National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) Guidance for Anaphylaxis Diagnosis 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., dyspnoea, 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., dyspnoea, 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: 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 18 years and above
3	Diagnosis of AD as defined by Hanifin and Rajka 1980 criteria for AD
4	History of AD for 1 year or more
5	Subjects with a history within 1 year prior to screening of inadequate response to treatment with topical medications or subjects for whom topical treatments are otherwise medically inadvisable
6	AD involvement of 10% (or more) body surface area at screening and baseline (visit 3) according to component A of SCORAD
7	EASI score of 20 (or more) at screening and baseline
8	An IGA score of 3 or more at screening and at baseline
9	A Worst Daily Pruritus numeric rating scale average score of 4 or more during the week prior to baseline
10	Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation
11	Women of child-bearing potential must use a highly effective form of birth control, confirmed by the investigator, throughout the trial and at least for 16 weeks after last administration of IMP
12	Documented history of either no previous CSA exposure and not currently a candidate for CSA treatment OR previous exposure to CSA in which case CSA treatment should not be continued or restarted

No.	Exclusion criteria
1	Subjects for whom TCSs are medically inadvisable in the opinion of the investigator
2	Concurrent enrolment in another interventional clinical trial
3	Previous randomisation in a tralokinumab trial
4	Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis
5	Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD
6	Use of tanning beds or phototherapy (NBUVB, UVB, UVA1, PUVA), within 6 weeks prior to randomisation

7	Treatment with immunomodulatory medications or bleach baths within 4 weeks prior to randomisation
8	Treatment with 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	Receipt of any investigational non-biologic agent within 5 half-lives prior to randomisation
12	Receipt of blood products within 4 weeks prior to screening
13	Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period
14	Known or suspected hypersensitivity to any component of the IMP or AxMP formulation
15	History of any active skin infection within 1 week prior to randomisation
16	History of a clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to randomisation
17	A helminth parasitic infection within 6 months prior to the date informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy
18	History of anaphylaxis following any biological therapy
19	History of immune complex disease
20	History of cancer
21	Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care
22	History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications
23	History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator
24	History of attempted suicide or at significant risk of suicide (either in the opinion of the investigator or on the C-SSRS)
25	Any disorder which is not stable and in the investigator's opinion could affect the safety of the subject, influence the findings of the trial, or impede the subject's ability to complete the trial
26	Any abnormal finding which in the investigator's opinion may put the subject at risk, influence the results of the trial, or influence the subject's ability to complete the trial
27	Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level 2.0 times the ULN (upper limit of normal) or more at screening

28	Positive HBsAg, HBsAb, HBcAb, or anti-HCV serology at screening. Subjects with positive HBsAb may be randomised provided they are hepatitis B vaccinated and have negative HBsAg and HBcAb
29	Subjects who are not willing to abstain from donating blood and/or plasma from the time of informed consent and for 16 weeks (5 half-lives) after last dose of IMP
30	Subjects who are legally institutionalised
31	Pregnant, breastfeeding, or lactating women
32	Employees of the trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals

Appendix 7: 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' 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

Signatory investigator

Prof. Dr. med PPD

PPD

, Germany

phone: +49 PPD

Appendix 8: Clinical Trial Protocol Addendum COVID-19

1 Rationale for clinical trial protocol addendum

The current COVID-19 pandemic warrants many subjects in the ECZTRA 7 trial to stay at home to comply with authority issued preventive measures. This make visits to the sites challenging, and in some cases impossible. To follow authorities restrictions and to safeguard the subjects in ECZTRA 7 as well as providing continued therapy to secure the scientific integrity, this clinical trial protocol addendum is installed to provide an opportunity for subjects to continue treatment with tralokinumab via home-use (self-injection).

No safety issues have been observed in subjects who applied home-use of IMP after training by site staff in previous or ongoing clinical trials with tralokinumab. Therefore, no safety issues are expected regarding home-use of IMP in ECZTRA 7.

2 GCP statement

Normal GCP procedures are followed for this protocol addendum. Subjects will be verbally informed and verbally consent to providing contact details (name, address, and telephone number) for shipping purposes.

3 eCRF recording

It must be recorded in the eCRF if the visit was conducted as a home-visit.

If the subject is reached by telephone/video contact and collection of AEs, concomitant medication and pregnancy test result (if applicable) are assessed, “Visit date” must be documented in the eCRF. All other assessments should be marked “Not done”. The log line “If not done, specify reason” must be answered with “COVID-19”. In addition, in the “Comments log”, one log line per visit should be entered with “COVID-19” – as reason for only partly performed assessments at the visit.

If no contact can be established between site and subject at a given visit, this must be recorded as a missed visit in the eCRF (“Not done”). The log line “If not done, specify reason” must be answered with “COVID-19”.

4 Description of visit scenarios

Without compromising the safety of subjects and site personnel, it is expected that efforts are made to secure attendance at sites for the Week 16 and Week 26 visits, securing important efficacy and safety assessments for the trial. Dependant on national guidelines regarding

COVID-19 and subject preferences, the remaining visits can follow three different scenarios as described below:

1) The subject is not restricted from attending visits at the clinic and continue to follow all procedures specified in the protocol.

2) The subject is still able to come to the clinic, but may foresee difficulties attending visits to the clinic going forward. In this case the following procedures must take place and be document in source documentation:

    a. Subject is verbally informed using the Participant Information Sheet and agrees to home-use of IMP.

    b. Site staff allocates IMP and TCS for subject using the EDC system (RAVE®) for the current visit + 2 additional visits.

    c. Subject is trained by site staff in home-use of IMP (see Section 5.1) by the unblinded HCP. The subject then self-injects IMP under supervision of the unblinded HCP. The remaining part of the visit takes place as per protocol.

    d. Site staff provide the following items to the subject:

        i. Participant Information Sheet for home use.

        ii. Instructions for Use.

        iii. Log of Drug Administration.

        iv. The proper amount of IMP (see bullet c) in a cooling bag.

        v. The proper amount of TCS (see bullet c).

        vi. One sharp-bin container.

        vii. Sanitisers: alcohol wipes, cotton balls or gauze.

        viii. For female subjects of child-bearing potential: one urine pregnancy test kit and Urine Pregnancy Test Instruction.

    e. The following visits must be conducted via phone with collection of AEs, assessment of concomitant medication, and urine pregnancy test results (if applicable) before IMP is self-injected. The subject is reminded to complete the eDiary and to start using the TCS tubes allocated for the next period.

3) Subject is not able to attend visits at the clinic:

   a. Site staff informs subject about the possibility of home-use as described in the Participant Information Sheet for home-use.

   b. Subject is verbally informed about home-use of IMP and verbally consents to providing contact details (name, address, and telephone number) to the courier for shipping purposes.

   c. Site staff allocates IMP and TCS for subject using the EDC system (RAVE®) for the 3 visits. In case needed, IMP and TCS can be dispensed for one additional visit.

   d. Site staff sends the following items by a LEO-approved courier company:

      i. Participant Information Sheet for home use.

      ii. Instructions for Use.

      iii. Log of Drug Administration.

      iv. The proper amount of IMP (see bullet c) in a cooling bag.

      v. The proper amount of TCS (see bullet c).

      vi. One sharp-bin container.

      vii. Sanitisers: alcohol wipes, cotton balls or gauze.

      viii. For female subjects of child-bearing potential: one urine pregnancy test kit and Urine Pregnancy Test Instruction.

   e. Site staff contacts the subject (by video-call) and ensures the following:

      i. Confirms that the Participant Information Sheet has been read, understood, and agreed to.

      ii. Subject is asked about pregnancy test outcome, concomitant medication use, and adverse events.

      iii. Subject is being instructed in home-use of IMP.

      iv. The subject self-injects IMP under supervision of the site staff.

v. The subject is reminded to complete the eDiary and to start using the TCS tubes allocated for the next period.

f. Site staff documents all of the above in the medical record at the clinic.

g. Site staff enters all available information into the EDC system (RAVE®), see Section 3.

5 Home-use of IMP

5.1 Subject training in self-injections of tralokinumab

Subjects will have the option to self-inject tralokinumab after adequate training by the investigator or delegated site staff. If the subject is a health care professional or has previous experience with SC-injections as judged by the investigator, training is limited to handling the IMP according to the Trial Product Handling Manual and procedures to be followed in case of an emergency.

The subject must inject tralokinumab under supervision by the trainer on one or more occasions such that the trainer is satisfied with the individual's understanding and confidence of the procedure. The subject will also be trained in filling out the Log of Drug Administration.

5.2 Injections of tralokinumab

Prior to self-injection at home, the subject will receive proper training in SC injection technique and on procedures to be followed in case of an emergency during or following home-use of tralokinumab. Tralokinumab will be injected by the subject when AE assessments have been completed.

All IMP self-injections need to be documented in the eCRF with 'COVID-19' written in the comments log for the visit in scope.

Subjects who misses one or more doses need to be documented in the eCRF with 'COVID-19' written in the comments log for each visit in scope.

Further details on IMP-injection are provided in the Trial Product Handling Manual. Subjects will also receive a pamphlet with instructions for IMP home-use and a Log of Drug Administration.

5.2 TCS

The use of TCS is described in the ECZTRA 7 clinical trial protocol and does not change with this document.

5.3 Emollients

The use of emollients is described in the ECZTRA 7 clinical trial protocol and does not change with this document.

6 Urine pregnancy tests

The schedule of pregnancy testing does not change with this document. However, the subjects need to perform the urine pregnancy test at home using the kit delivered by the site. The subject will also be provided with a Urine Pregnancy Test Instruction. Results should be communicated to the site and documented in the eCRF and source documents.

7 Supporting documents (LEO Pharma use only)

Document	eTMF ID
ECZTRA 7 Clinical Trial Protocol	000064964
Trial Product Handling Plan	000105963
Patient Information Sheet for Home-use	000296864
Instructions for IMP home-use (pamphlet)	000077966
Log of Drug Administration	000298224
Urine Pregnancy Test Instruction	000298227

Appendix 9: Clinical Trial Protocol Addendum no. 2 *Imagine for Studies*

1 Rationale for clinical trial protocol addendum

The current COVID-19 pandemic warrants many subjects in the ECZTRA 7 trial to stay at home to comply with authority-issued preventive measures. This makes visits to the sites challenging, and in some cases impossible. This clinical trial protocol addendum is installed for subjects who cannot come to the site for the Week 26 visit and who have provided informed consent for using the mobile application called '*Imagine for Studies*' for remote collection of data related to efficacy of tralokinumab.

No safety issues are expected as a consequence of this clinical trial addendum.

2 GCP statement

Normal GCP procedures are followed for this protocol addendum. Subjects will be verbally informed and verbally consent to the site staff providing contact details (name, address, and telephone number) for sending the necessary information about *Imagine for Studies* to subjects via courier.

The subjects sign the Participant Information Sheet after having ample time to consider participation. The site staff will not sign the Participant Information Sheet.

Precautionary steps have been taken to secure the integrity of the trial and the confidentiality of the identity of the subjects via a controlled data transfer between two separate units of LEO Pharma: LEO iLab (including a team of certified dermatologists) and LEO Clinical Operations. In this manner, the GCP adherence described in the clinical trial protocol and the ICF signed at screening remains intact and unchanged.

The procedures described in this addendum are considered well-balanced and proportionate, taking into account the legitimate interest of trial sites in avoiding further burden in terms of time and staffing during the COVID-19 pandemic (1).

3 Roles and responsibilities

The following responsibilities have been assigned to all parties involved in the processes described in this protocol addendum (see **Table 1**).

Table 1 Roles and responsibilities

Role	Responsibilities	Reference
LEO Clinical Operations	• Overall responsible for the ECZTRA 7 trial conduct and reporting	Section 5.4
LEO iLab	• Handles all data from the *Imagine for Studies* app and sends data without potential subject identifiers to LEO Clinical Operations • Technically responsible for the *Imagine for Studies* app (including user support) • Provides username and password to site staff • Manages a team of certified dermatologists who evaluate the photos using remote EASI scores	Section 5.4
Site staff	• Manages the informed consent process • Sends written information material to the subject • Provides subject login details (password and username) for the *Imagine for Studies* app	Section 4
Subject	• Provides verbal informed consent to use the *Imagine for Studies* app • Signs the Participant Information Sheet and returns it at the next possible site visit	Section 4
	• Uses the app as instructed	Participant Guidance Booklet
NL-CRA	• Submits clinical trial protocol addendum and supporting documents to the relevant ethical committees and competent authorities as per local regulations • Supports site staff with information material to the subjects	Section 2

4 Information to trial sites

If a subject cannot come to the site for the Week 26 visit, the site staff should initiate remote collection of efficacy-related outcomes using the *Imagine for Studies* app by following the steps below:

1) Site staff informs the subject about the possibility of remote collection of efficacy-related outcomes using the *Imagine for Studies* app as described in the Participant Information Sheet.

2) Subject is verbally informed about the *Imagine for Studies* app and verbally consents to providing contact details (name, address, and telephone number) to the courier.

3) Site staff sends the following items by the courier:

    a. Participant Information Sheet.
    b. Participant Guidance Booklet.

4) Site staff contacts the subject and ensures that the subject has had ample time to consider the written content in the Participant Information Sheet and the Participant Guidance Booklet.

    a. If verbal consent is obtained, the site staff documents this in the medical record.
    b. Subject signs the Participant Information Sheet and returns it at the next possible site visit.

5) Site staff completes all remote assessments as described in the previous clinical trial protocol addendum (for COVID-19) and ensures that the subject is able to complete data collection via the *Imagine for Studies* app.

6) Site staff documents all of the above in the medical record at the site.

5 Remote collection of data related to efficacy of tralokinumab using the *Imagine for Studies* app

The *Imagine for Studies* app is a digital solution that has been developed by LEO iLab specifically for the ECZTRA 7 trial and provided in local language. Subjects that are not able to attend the Week 26 visit at the site and who have given informed consent to use the *Imagine for Studies* app can upload photos of their skin lesions from selected body areas (Section 5.2) as well as answering a questionnaire about the extent of AD (Section 5.3).

5.1 Installation and login procedure

The subject downloads the *Imagine for Studies* app and follows the instructions provided in the Participant Guidance Booklet. For questions and support, please see Section 5.5. The screens for installation and login are presented in **Figure 1** below.

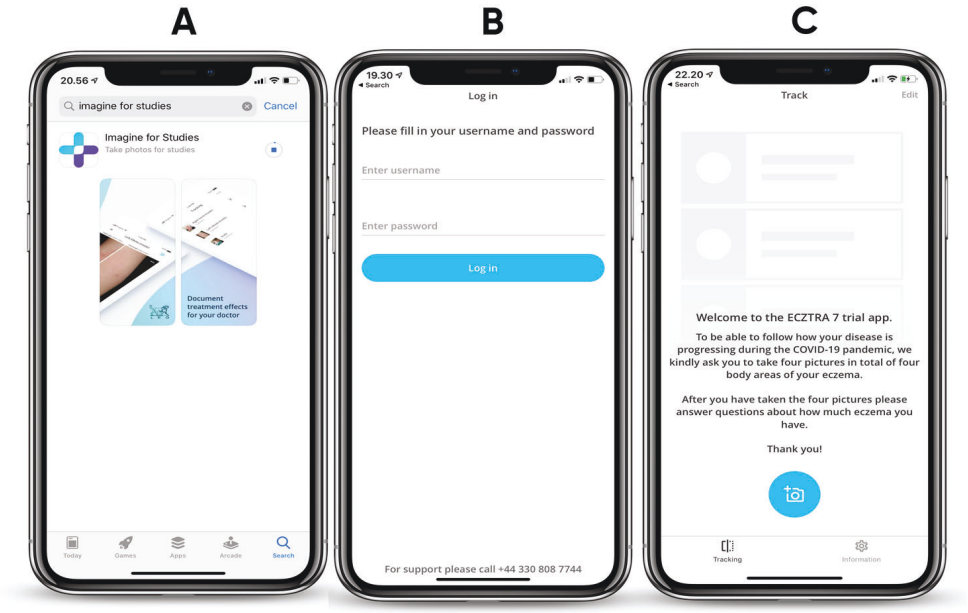


Figure 1 Installation and login procedure

- **A.** Download of the *Imagine for Studies* app.
- **B.** Login frontpage: Username and password must be filled in here.
- **C.** Welcome page "Welcome to the ECZTRA 7 trial app. To be able to follow how your disease is progressing during the COVID-19 pandemic, we kindly ask you to take four pictures in total of four body areas of your eczema. After you have taken the four pictures please answer questions about how much eczema you have. Thank you!".

5.2 Taking photos of the skin

Subjects will take 4 photos as described below at the time of the planned Week 26 visit before applying any moisturiser.

- One photo of eczema on the head or neck
- One photo of eczema on one arm
- One photo of eczema on either the stomach, chest, or back
- One photo of eczema on one leg

It is very important that the subject takes all 4 photos.

The subject will be asked to upload a photo of normal healthy skin if there is no visible eczema in one of the four body areas. Furthermore, the photos are to be taken in a prioritised order as follows:

- If there are multiple skin lesions of eczema in one body area, the lesion with the most redness should be chosen.
- If there are multiple lesions with the same level of redness in one body area, the lesion with the most redness and oozing should be chosen.

If the photo is of substandard quality, LEO iLab will ask the NL-CRA to inform the site staff, who then contacts the subject and asks for a new photo to be upload.

Figure 2 illustrates how the subject selects one body area at a time and captures a photo of the skin. The Participant Guidance Booklet outlines tips and best practices for ensuring adequate photo quality.

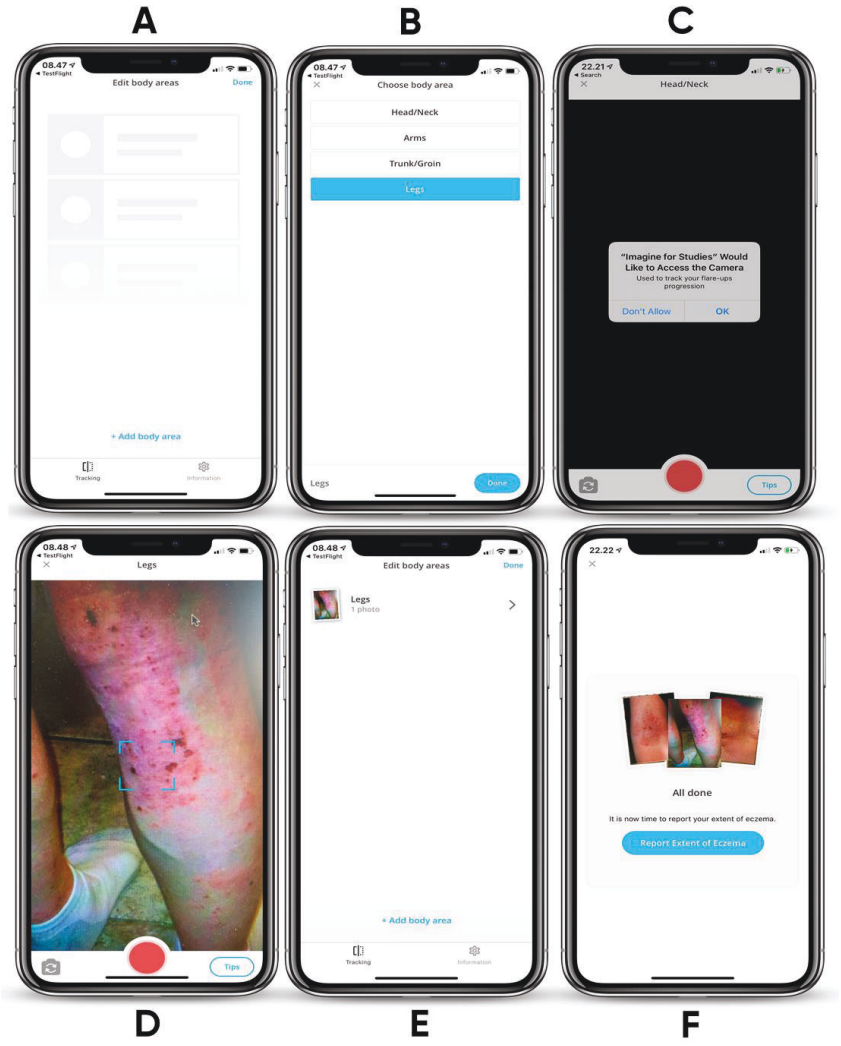


Figure 2 Taking photos of the skin

- **A.** Screen menu 'Edit body areas'. The function 'Add body area' is selected to proceed.
- **B.** Screen menu 'Choose body area'. Here, the body areas 'Head/Neck, Arms, Trunk/Groin, or Legs' can be chosen.
- **C.** The *Imagine for Studies* app requests permission to access the camera. 'OK' must be selected to proceed.
- **D.** A photo of the skin is taken according to the body area selection made in (B). The photo can be retaken or accepted (not shown).
- **E.** The photo assigned to the body area is saved, and a new body area can be selected by choosing 'Add body area'. This takes the subject back to the menu in (B), where a new body area must be selected. The steps (B-E) are repeated until 4 photos, 1 for each body area, are saved.
- **F.** Screen with the text: "All done. It is now time to report your extent of eczema". The subject then proceeds to the questionnaire by selecting 'Report Extent of Eczema'.

5.3 Questionnaire about the extent of atopic dermatitis

The questionnaire in the *Imagine for Studies* app allows the subject to evaluate the percentage of a selected body area that is covered by AD lesions on a scale from 0–100%. Each body area accounts for 100%. The subjects will be presented for the following text in the app provided in local language. **Figure 3** shows the questionnaire with guiding illustrations of the relevant body parts.

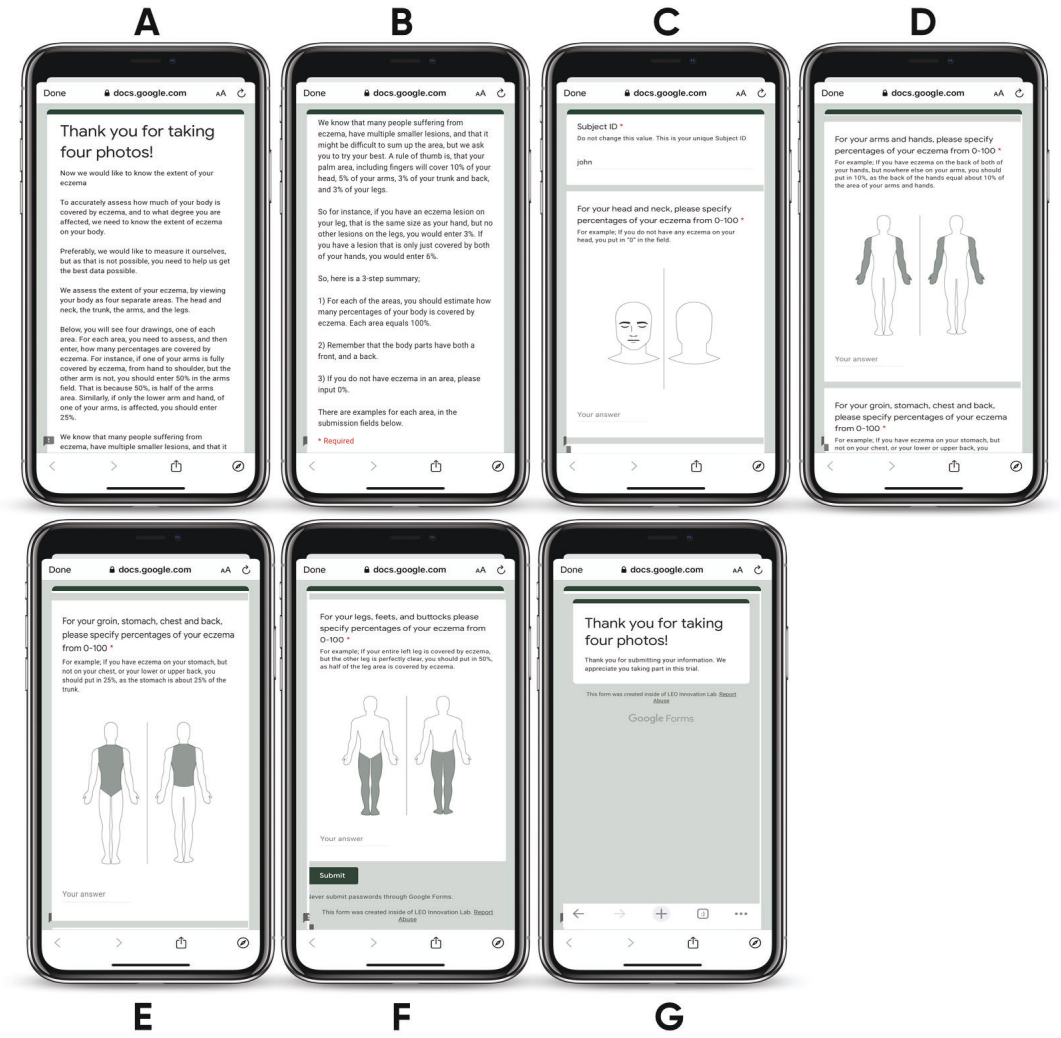


Figure 3 Questionnaire about the extent of atopic dermatitis
The texts of the screens (A-G) are copied below.

A-B Thank you for taking four photos! Now we would like to know the extent of your eczema. To accurately assess how much of your body is covered by eczema, and to what degree you are affected, we need to know the extent of eczema on your body.

We assess the extent of your eczema, by viewing your body as four separate areas. The head and neck, the trunk, the arms, and the legs. Below, you will see four drawings, one of each area. For each area, you need to assess, and then enter, how many percentages are covered by eczema. For instance, if one of your arms is fully covered by eczema, from hand to shoulder, but the other arm is not, you should enter 50% in the arms field. That is because 50%, is half of the arms' area. Similarly, if only the lower arm and hand of one of your arms is affected, you should enter 25%.

We know that many people suffering from eczema, have multiple smaller lesions, and that it might be difficult to sum up the area, but we ask you to try your best. A rule of thumb is that your palm area, including fingers will cover 10% of your head, 5% of your arms, 3% of your trunk and back, and 3% of your legs. So for instance, if you have an eczema lesion on your leg, that is the same size as your hand, but no other lesions on the legs, you would enter 3%. If you have a lesion that is only just covered by both of your hands, you would enter 6%. So, here is a 3-step summary (1) For each of the areas, you should estimate how many percentages of your body is covered by eczema. Each area equals 100% (2) Remember that the body parts have both a front, and a back (3) If you do not have eczema in an area, please input 0%. There are examples for each area in the submission fields below.

C Subject ID. Do not change this value. This is your unique Subject ID. For your head and neck, please specify percentages of your eczema from 0-100. For example; If you do not have any eczema on your head, you put in "0" in the field.

D For your arms and hands, please specify percentages of your eczema from 0-100. For example; If you have eczema on the back of both of your hands, but nowhere else on your arms, you should put in 10%, as the back of the hands equal about 10% of the area of your arms and hands.

E For your groin, stomach, chest and back, please specify percentages of your eczema from 0-100. For example; If you have eczema on your stomach, but not on your chest, or your lower or upper back, you should put in 25%, as the stomach is about 25% of the trunk.

F For your legs, feet, and buttocks please specify percentages of your eczema from 0-100. For example; If your entire left leg is covered by eczema, but the other leg is perfectly clear, you should put in 50%, as half of the leg area is covered by eczema.

G Thank you for submitting your information. We appreciate you taking part in this trial.

5.4 Data flow

The key principles for how data flows from the subject using the *Imagine for Studies* app to the reporting in the CTR are showed in **Figure 4** and briefly explained below.

All data collected via the *Imagine for Studies* app are stored on secure (GDPR and HIPAA compliant) AWS servers managed by LEO iLab. The data captured will include potential subject identifiers, such as photos of the facial region as well as information about the extent of AD. Therefore, precautionary steps have been taken to ensure that LEO Clinical Operations at no point in time will have access to data with potential subject identifiers.

The photos will be evaluated by a team of certified dermatologists within LEO iLab who have no connections to LEO Clinical Operations. The outcome of the evaluation will be a remote

EASI score, one score for each subject. The EASI principles used to assess a remote EASI score is based on the HOME working group definitions (2).

The remote EASI scores and the questionnaire data will together form the data transfer that does not include photos (i.e. potential subject identifiers). The data transfer delivered by LEO iLab to the SDTM database within LEO Clinical Operations will take place before database lock. An ADAM dataset is then derived from the SDTM database and used for statistical reporting. The data generated from the *Imagine for Studies* app will not be part of the pre-specified analysis, but rather serve as a supplement to handling the missing data at Week 26. All data obtained from *Imagine for Studies* will be deleted from the LEO iLab secure server before finalisation of the CTR.

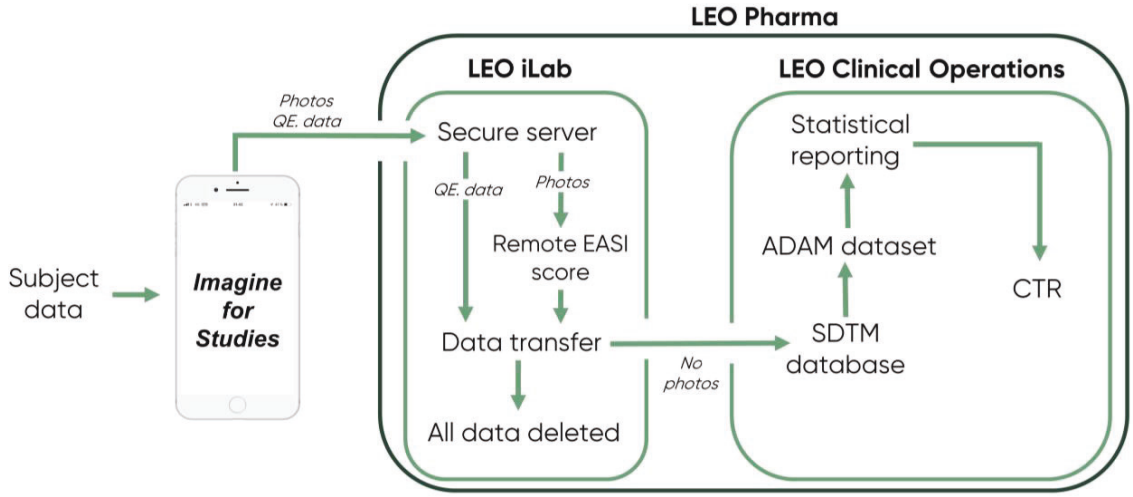


Figure 4 Data flow from the *Imagine for Studies* mobile application to final clinical trial report.

Abbreviations: AD = atopic dermatitis; ADAM = analysis data model; CTR = clinical trial report; SDTM = study data tabulation model; QE = questionnaire.

5.5 Questions and support

The subject will be asked to contact the site staff regarding questions related to the *Imagine for Studies* app. The site staff may contact LEO iLab via one of the telephone numbers listed in the Participant Guidance Booklet if support is needed. Translator service is available for all countries in scope for this ECZTRA 7 clinical trial protocol addendum.

6 Supporting documents (LEO Pharma use only)

Document	eTMF ID
ECZTRA 7 Clinical Trial Protocol	000064964
Patient Information Sheet (*Imagine for Studies*)	000316466
Participant Guidance Booklet	000316469

7 References

1. EMA. European Medicines Agency. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic. Version 3. 2020.
2. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001;10(1):11-18.

Appendix 10: Protocol amendment history

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

Amendment 2 (19-Aug-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 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 is the addition of photographs to the trial assessments. Furthermore, clarifications on the required qualifications of the principal investigator as well as on prohibited medications during the trial are provided.

Additional changes included in the amendment are also presented in the table below.

Note: The table below describes 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	Schedule of trial procedures has been updated to include photographs.	To add a photography component to assessments to show disease progression over time.
Section 11.1 Overview	Photographs have been added to the list of trial procedures.	
Section 11.6.1 Photography	**At selected trial sites, subjects will be asked to participate in a photography component involving digital photography assessments to show disease progression over time.**	

Section no. and name	Description of change	Brief rationale
	Participation in this photography component requires that the subject provides additional informed consent. **Digital colour photographs will be taken of the disease area and representative lesions at 4 different time points according to the schedule of trial procedures (Section 4).** **Custom photography equipment will be delivered to trial sites by the central photography vendor together with a photography manual. Photography standards and procedures are provided in the manual. The photographs will have no other subject identifier than the subject ID and will be transmitted electronically to the photography vendor using a secure file transfer protocol.** **Printed copies of the photographs must be included as part of the individual subject source documentation.** **LEO may at its discretion use the photographs in publications, posters and similar types of information material or media targeting patients and HCPs. The photographs can also be part of**	

Section no. and name	Description of change	Brief rationale
	training material used for training and educational purposes. Steps will be taken to ensure that the identity of the subject is protected to the extent possible.	
Section 9.5 Rescue treatment Section 10.2.2 Reasons for temporary discontinuation of IMP	If a subject receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (~~CSA~~, methotrexate, mycophenolate mofetil, azathioprine~~,~~ ~~dupilumab~~, etc.), IMP will be immediately discontinued (see Section 10.2.2). After the treatment with these medications is completed, IMP may be resumed if deemed appropriate by the investigator, but not sooner than 5 half-lives after the last dose of systemic rescue treatment. The use of biological rescue treatment will be disallowed for the entire trial duration. Treatment with systemic corticosteroids or non-steroidal immunosuppressive/immunomodulating medications (e.g.~~, CSA~~, 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.	To reflect that subjects have either failed on previous CSA treatment or CSA is contraindicated as per inclusion criterion. Therefore, CSA is not applicable as rescue treatment.
Section 9.7 Prohibited medications and	The panel with prohibited medications and procedures in the previous version of the protocol has been replaced with a	To ensure clear instructions on prohibited medications and procedures to investigators.

Section no. and name	Description of change	Brief rationale
procedures	text description.	The content and meaning of the section has not been changed, only the presentation of information for increased readability.
Section 11.1 Overview	Subjects participating in the trial will be under careful supervision of a **qualified** principal investigator ~~who must be dermatologist or allergist~~ **(see Appendix 1.4)**.	To reflect that the principal investigator or investigator does not have to be a certified dermatologist or allergist to conduct the trial.
Throughout	Global Pharmacovigilance has been changed to Global Safety.	To reflect a change of department name within LEO Pharma.
Throughout	Minor editorial and document formatting revisions.	Minor, have therefore not been summarised.

Amendment 1 (13-Nov-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 main reason for the amendment is to introduce the possibility for eligible subjects in selected countries to participate in a long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]) without completing the safety follow-up period in the present trial. Indeed, a new anti-drug antibodies (ADA) assay has been developed with improved tralokinumab tolerance. This means that the presence or absence of ADA can be determined in serum samples with tralokinumab present. Previously, this was not possible and therefore ADA sampling at the end of the 14-week off-treatment safety follow-up was originally required for the ADA evaluation. Thus, in selected countries, the new ADA assay will allow eligible subjects who have completed the treatment periods of the present trial to continue into the long-term extension trial without completing the safety follow-up period in the present trial. These subjects will have their safety follow-up period after end of treatment in the long-term extension trial.

Additional changes included in the amendment are also presented in the table below.

Note: The table below describes 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 Protocol synopsis Section 4 Schedule of procedures Panel 3 (footnote 2) Section 7.1 Overall trial design Section 7.3 End of trial definition Section 9.9 Provision for subject care following trial completion	Subjects will have a final safety follow-up visit 16 weeks after the last dose of IMP (which is also considered the end-of-trial visit), except subjects who enter the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]). The subjects may enter ECZTEND at any time during the off-treatment safety follow-up period. For these subjects, the end-of-trial visit will be the last visit in the present trial. The subjects entering ECZTEND after completion of the end-of-treatment visit (Week 26) will also be considered as trial completers. For all subjects assigned treatment, an end-of-treatment form and end-of-trial form will be completed in the eCRF.	To clarify that eligible subjects (in selected countries) who have completed the treatment periods of the present trial may continue into the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]) without completing the safety follow-up period.

Section no. and name	Description of change	Brief rationale
Section 8.3 Exclusion criteria Appendix 6 Eligibility criteria	Known or suspected allergy or reaction to any component of the IMP **or AxMP** formulation.	To clarify that components of the AxMP is also taken into account.
Section 11.1 Overview	Order of patient-reported outcomes (PROs) revised.	To match the order by which the PROs appear in the reporting device used by the subjects at the trial site.
Section 11.4.1	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 13.2 Collection of adverse events	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 injection of IMP). **For subjects entering the long-term extension**	To clarify how (S)AEs occurring in subjects entering LP0162-1337 (ECZTEND) will be collected if visits in LP0162-1346 overlap with visits in ECZTEND.

Section no. and name	Description of change	Brief rationale
	trial (LP0162-1337, ECZTEND), any (S)AE with onset before the final visit in LP0162-1346 should be reported in LP0162-1346. If ongoing, the (S)AE will also be recorded as medical history in ECZTEND.	
Section 13.6.1 Adverse events of special interest Panel 12	The text in the heading of the right column was modified as follows: Additional information to be provided **(if available[1])** A footnote was 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 additional information regarding the adverse events (AEs) of special interest is to be provided only if available, and that it is not a requirement.
Section 14.3.9.1 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 or permanent discontinuation of IMP will be **tabulated and** listed.	Tabulation and listings are considered a more practical and informative way of presenting AESIs. This will enable easier overview of the individual cases as well as sorting and pooling of data from other trials.

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

Signature Page for TMF-000064964 v5.0

Reason for signing: Approved	Management / Lead Approver Verdict(s) Name: PPD Capacity: Medical Date of signature: 16-Jun-2020 11:26:20 GMT+0000

Reason for signing: Approved	Management / Lead Approver Verdict(s) Name: PPD Capacity: Medical Date of signature: 16-Jun-2020 18:36:54 GMT+0000

Reason for signing: Approved	Management / Lead Approver Verdict(s) Name: PPD Capacity: Biostatistics Date of signature: 16-Jun-2020 19:48:18 GMT+0000

Reason for signing: Approved	Manag Name: PPD Capacity: Clinical Date of signature: 17-Jun-2020 09:48:29 GMT+0000

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