Dermatology beyond the skin

Cover Page

Official title: Tralokinumab monotherapy for moderate-to-severe atopic dermatitis ECZTRA 1 (ECZema TRAlokinumab trial no. 1)
LEO Pharma number: LP0160-1325
NCT number: NCT03131648
Date: 14-Aug-2018

Updated Clinical Trial Protocol

LP0162-1325

Tralokinumab monotherapy for moderate-to-severe atopic dermatitis

ECZTRA 1 (ECZema TRAlokinumab trial no. 1)

Phase 3 - Efficacy and safety trial

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

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

LEO Pharma A/S	**Trial ID:**	**LP0162-1325**
	Date:	**14-Aug-2018**
	EudraCT No:	**2016-004200-65**
	Version:	**4.0**

1 Clinical trial protocol statement

1.1 Approval statement LEO Pharma A/S

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

PPD, MSc Stat
Biostatistics Lead, Global Clinical Operations

PPD, MD, PhD
Medical Lead, Medical Sciences and Safety

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

1.2 Approval statement international coordinating investigator

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

The following person has approved this clinical trial protocol:

Andreas Wollenberg, Prof. Dr. med. Dr. h.c.
International coordinating investigator

1.3 Acknowledgement statement investigator(s)

Each participating investigator must agree to the approved clinical trial protocol and consolidated clinical trial protocol(s) comprising any subsequent amendment(s) by signing a Clinical Trial Protocol Acknowledgement Form or a similar document.

Protocol amendment summary of changes table

Document history	Date	Type of amendment
Amendment 3 (substantial)	14-Aug-2018	Global
Amendment 2 (substantial)	12-Dec-2017	Global
Amendment 1 (substantial)	28-Aug-2017	Global
Original protocol	03-Mar-2017	

Amendment 3 (14-Aug-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 (33).

Overall rationale for the amendment

The main reason for the amendment is that a new anti-drug antibody (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, the new ADA assay will allow eligible subjects who have completed the treatment periods of trial LP0162-1325 to continue into the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]) 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.

In addition, the amendment includes other changes, as 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 number and name	**Description of change**	**Brief rationale**
Section 4 Schedule of procedures (SoP), Panel 2 (footnote 3), Panel 3 (footnote 2) and Panel 4 (footnote 2); Section 7.1 Overall trial design; Section 7.3 End of trial definition	Subjects will have a final safety follow-up visit 16 weeks after the last dose 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]). 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 trial LP0162-1325. The subjects entering ECZTEND after completion of the end of treatment visits (Week 52 or Week 68) 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 who have completed the treatment periods of trial LP0162-1325 may continue into the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]) without completing the safety follow-up period.
Section 4 Schedule of procedures (SoP), Panel 2 (footnote 5), and Panel 4 (footnote 3); Section 7.1 Overall trial design; Section 9.2 Administration of investigational medical products	Subjects eligible for home-use will receive proper training at 3 dosing visits in the open-label period after additional consent has been obtained.	To clarify what is considered proper training of the subjects or caregivers in home-use (that is 3 dosing visits during open-label treatment).

Section number and name	**Description of change**	**Brief rationale**
Section 9.5 Concomitant medication and procedures;	**In addition, the use of topical treatments is permitted during safety follow-up (from Week 52 or Week 68) at the investigator's discretion.**	To clarify that the use of topical treatments is permitted during the safety follow-up period.
Section 9.7 Rescue treatment	From Week 16 through safety follow-up (FU1 [Week 66] or FU2 [Week 82]) subjects may use mild to moderate strength TCS **and/or TCI** as needed (prn usage) on lesional skin at the investigator's discretion (see Appendix 9 for TCS classification and examples). Use of ~~such~~ TCS **and TCI** should be recorded as concomitant medication.	To clarify that subjects in the open-label tralokinumab arm are allowed to use TCS as well as TCI.
Section 9.9.2 Storage of IMPs	The IMP must be stored at 2 to 8°C at the site. The temperature during storage must be monitored by a calibrated, stationary, and continuously **monitoring** ~~recording~~ system. Minimum requirement is a calibrated min/max thermometer.	To clarify that the storage of IMP will be monitored.
Section 9.9.3 Drug accountability	Used syringes will be destroyed at the trial site provided the trial site has procedures in place for such IMP destruction~~; this requires that the trial site is able to issue a certificate documenting the kit number(s) that were destroyed~~. Trial sites which do not have such IMP destruction procedures in place will dispose used syringes in sharps bins which will be shipped to the contract manufacturing organisation (CMO)~~ at the end of the trial~~. **For more information about IMP accountability, please refer to the IMP manual.**	To clarify that a certificate of destruction is not required for used IMP. To also allow shipment of sharps bins to the CMO during the trial.
Section 10.3.2.8 EQ-5D-5L	The second section consists of a vertical visual analogue scale anchored at 0 ('the **worst** ~~best~~ health you can imagine') and 100 ('the **best** ~~worst~~ health you can imagine').	To correct the definition of extremes in the vertical visual analogue scale.

Section number and name	**Description of change**	**Brief rationale**
Section 10.5.2 Serum biomarkers	The biomarker results from the small panel will be presented in the CTR, whereas results from the large panel (assessed at selected trial sites) will be presented in a separate report.	To clarify that the results from the small biomarker panel will be included in the CTR.
Section 10.5.3 Skin biopsies (selected trial sites)	Global gene expression analysis by **RNA sequencing**~~microarray~~. **Overall, t**~~T~~he results from the analyses of biopsy material will ~~not~~ be included in the CTR, **except the global gene expression analysis which** ~~but~~ will be presented in a separate report.	To clarify that global gene expression analysis will be carried out by RNA sequencing and that the results from this analysis will not be included in the CTR.
Section 11.1 Collection of adverse events;	AEs must be collected from time of first trial-related activity after the subject has signed the informed consent form until completion of the clinical trial (defined as the safety follow-up visit 16 weeks after last injection). **For subjects entering the long-term extension trial (LP0162-1337, ECZTEND), any (S)AE with onset before the final visit in LP0162-1325 should be reported in LP0162-1325. If ongoing, the (S)AE will also be recorded as medical history in ECZTEND**.	To clarify how (S)AEs occurring in subjects entering ECZTEND will be collected if visits in LP0162-1325 overlap with visits in ECZTEND.
Section 11.5.1 Adverse events of special interest Panel 13 (Footnote 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 is to be provided only if available and is not a requirement.
Section 12.3.7 Analysis of safety	Adverse events of special interest (AESIs) will be tabulated and listed instead of being presented in a narrative.	Tabulation and listings are considered a more practical and informative way of presenting data on AESIs. This will enable easier overview of the individual cases as well as sorting and pooling of data from several trials.

Section number and name	**Description of change**	**Brief rationale**
Section 12.3.7.5 Anti-drug antibodies	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. ~~Samples positive for nAb to tralokinumab are then titrated to determine relative amounts of nAb present in each test sample.~~	To reflect that titre information will not be available from the nAB assay.
Appendix 1 Protocol summary	Updated with the changes described above, as applicable.	To reflect updated text in the protocol.
Appendix 7 Country-specific requirements	Section 9.9.3 Drug accountability **Used syringes will be destroyed at the trial site provided the trial site has procedures in place for such IMP destruction.** **Trial sites which do not have such IMP destruction procedures in place will dispose used syringes in sharps bins which will be shipped to the contract manufacturing organisation (CMO).** **In Japan, used syringes will be destroyed at the trial sites.**	To clarify that used syringes will be destroyed at the trial site in Japan.
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 antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BP	blood pressure
BSA	body surface area
CCL	C-C motif chemokine
CI	confidence interval
CMO	contract manufacturing organisation
CRA	clinical research associate
CRO	contract research organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	clinical trial report
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DPP4	dipeptidyl peptidase 4
EASI	Eczema Area and Severity Index
EASI50	At least 50% reduction in EASI score
EASI75	At least 75% reduction in EASI score
EASI90	At least 90% reduction in EASI score
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL 5-Dimension Health Questionnaire 5 Level
FU	follow-up visit
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HCP	healthcare professional

HQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification number
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IL	interleukin
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
LEO	LEO Pharma A/S
LOCF	last observation carried forward
nAB	neutralising antibodies
NRS	numeric rating scale
PDE-4	phosphodiesterase 4
PGI-B	Patient Global Impression of Bother
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetics
POEM	Patient Oriented Eczema Measure
PRO	patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
SAE	serious adverse event
SC	subcutaneous
SCORAD	Scoring Atopic Dermatitis
SCORAD50	At least 50% reduction in SCORAD score
SF-36	36-Item Short Form Health Survey
SoP	schedule of procedures
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
Th2	T-helper-2
TSQM	Treatment Satisfaction Questionnaire for Medication

ULN	upper limit of normal
UV	ultraviolet
WPAI-GH	Work Productivity and Activity Impairment – General Health

2 Trial identification

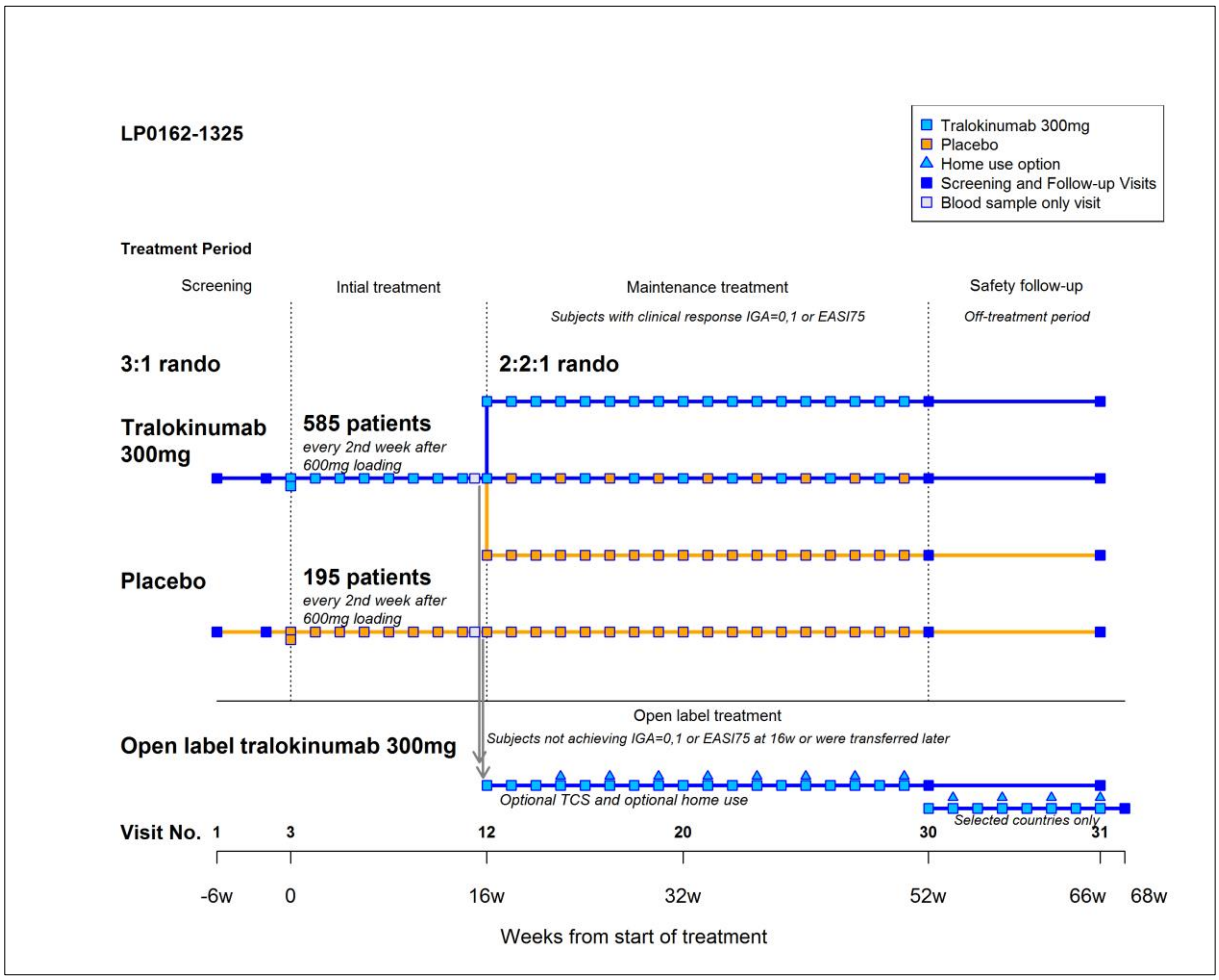
EudraCT number: 2016-004200-65

IND number: 123797

ClinicalTrials.gov number: NCT03131648

3 Schematic of trial design

Panel 1 Trial design



EASI 75, at least 75% reduction in EASI score; IGA, Investigator's Global Assessment; No, number; rando, randomisation; TCS, topical corticosteroid; w, week.

4 Schedule of procedures (SoP)

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

	Screening[1]		Initial treatment period									
Visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[2]**	**12[3]**
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**15**	**16**
Day	**-42**	**-14**	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**105**	**112**
Visit window (days)	**±3**	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Trial population and eligibility (Section 8 and Appendix 4B)												
Informed consents	X[4]											X[5]
Eligibility	X		X									
Trial products and randomisation (Section 9)												
Initiation of emollients (bcg. treatment)[6]		X										
Concomitant medication/procedures	X		X	X	X	X	X	X	X	X		X
Randomisation			X									X[7]
IMP administration and compliance			X[8]	X[8]	X[8]	X	X	X	X	X		X[7,8]
Investigator assessments at screening/baseline (Section 10.2)												
C-SSRS	X											
Demographics (age) and BSA	X		X									
Other demographics and medical history	X											
Height and weight			X									
Investigator assessments of efficacy (Section 10.3.1)												
IGA	X		X	X	X	X	X	X	X	X		X

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

	Screening[1]		Initial treatment period									
Visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[2]**	**12[3]**
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**15**	**16**
Investigator assessments of efficacy (Section 10.3.1)												
EASI	X		X	X	X	X	X	X	X	X		X
SCORAD	X		X	X	X	X	X	X	X	X		X
Subject assessments of efficacy (Section 10.3.2)												
eDiary training		X										
eDiary completion[9]		<- ========== ->										
POEM and DLQI			X	X	X	X	X		X			X
EQ-5D-5L and HADS			X		X		X		X			X
SF-36 and WPAI-GH			X				X					X
TSQM				X								X
Safety assessments (Sections 10.4 and 11)												
Vital signs	X		X[8]	X[8]	X[8]	X	X	X	X	X		X[8]
Physical examination	X		X				X					X
ECG	X		X				X					X
Serum pregnancy test	X											
Urine pregnancy test			X		X		X		X			X
Hepatitis B, C and HIV	X											
Serum chemistry, haematology, and IgE	X[10]		X		X		X		X			X
Urinalysis	X		X				X					X

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

	Screening[1]		Initial treatment period									
Visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[2]**	**12[3]**
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**15**	**16**
Safety assessments (Sections 10.4 and 11)												
Pharmacokinetics				X	X					X	X[2]	X
ADA			X		X							X
Adverse events	X	X	X	X	X	X	X	X	X	X		X
Other assessments (Section 10.5)												
Skin swabs (S. aureus)			X									X
Skin swabs (microbiome)[11]			X				X					X
Serum biomarkers (small panel)			X		X		X					X
Serum biomarkers (large panel)[11]			X		X		X					X
Skin biopsies[11]			X[12]		X							X
Photography[11]			X	X	X	X	X	X	X	X		X

1) For subjects who do not require a wash-out, visits 1 and 2 will be combined and screening will be reduced to 2 weeks; hence, these subjects will only attend visit 2 (Week -2) which will include all assessments shown under Week -6. Similarly, for subjects who only require a 2-week wash-out, screening visits 1 and 2 will be combined (Week -2). The screening period has a maximum duration of 6 weeks.

2) At Week 15, subjects will only have a blood sample drawn. No assessments that require trial personnel will be performed. Collection of AEs and reporting of concomitant medication and procedures will occur at the following trial visit.

3) Assessments performed at Week 16 are also to be done at an early termination visit and at a nominal Week 16 visit, if applicable. See Section 8.5 for further details. All subjects will have a final safety follow-up (FU1) 16 weeks after the last dose of IMP, except subjects who enter the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]). Subjects may enter ECZTEND at any time during the safety follow-up period (see Section 7.1). An end of treatment form and end of trial form must be completed in the eCRF for all subjects assigned treatment.

4) Additional informed consents are required for participation in (i) the exploratory component involving microbiome skin swab, large biomarker panel, and skin biopsy, and (ii) the photograph component (selected trial sites only).
5) Subjects who are eligible for home-use during open-label treatment will have to provide additional informed consent before the training at the site (Section 9.2); home-use will only commence after proper training of the subject or caregiver (at 3 dosing visits after the additional consent has been obtained) and after 3 doses of open-label tralokinumab administered at the trial site, i.e., starting no earlier than Week 22, depending on when the subject transfers to open-label treatment (selected countries only).
6) 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.
7) Subjects who achieve a clinical response (IGA 0/1 or EASI75) at Week 16 will be re-randomised into the maintenance period and then receive the first injections of maintenance treatment (Panel 3). Subjects that do not achieve clinical response at Week 16 will be transferred to open-label tralokinumab 300 mg Q2W treatment with optional use of TCS and then receive the first injections of open-label treatment (Panel 4).
8) For the first 3 IMP dosing visits in both the initial and open-label treatment period, subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later (Section 9.2).
9) The eDiary consists of (i) Eczema-related Sleep NRS, (ii) Worst Daily Pruritus NRS, (iii) Average Daily Pruritus NRS, (iv) PGI-B, and (v) PGI-S. The eDiary will be completed daily from Week -2 to Week 52.
10) IgE not assessed at screening.
11) Optional, selected trial sites only.
12) At baseline, a total of 4 skin biopsies will be taken (2 from lesional skin, 2 from non-lesional skin) at an anatomically similar site.

ADA, anti-drug antibodies; Bcg, background; BSA, body surface area; C-SSRS, Columbia-Suicide Severity Rating Scale; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI75, at least 75% reduction in EASI score; 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; NA, not applicable; NRS, numeric rating scale; PGI-B, Patient Global Impression of Bother; PGI-S, Patient Global Impression of Severity; POEM, Patient Oriented Eczema Measure; Q2W, every 2 weeks; SCORAD, Scoring Atopic Dermatitis; SF-36, 36-Item Short Form Health Survey; TSQM, Treatment Satisfaction Questionnaire for Medication; WPAI-GH, Work Productivity and Activity Impairment – General Health.

Panel 3 Schedule of trial procedures: maintenance treatment period and follow-up

	Maintenance treatment period																		FU1[2]
Visit	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30[1]**	**31**
Week	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**66**
Visit window (days)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Trial products (Section 9)																			
IMP administration and compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medication/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigator assessments of efficacy (Section 10.3.1)																			
IGA	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X	
EASI	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X	
SCORAD		X		X		X		X		X		X		X		X		X	
Subject assessments of efficacy (Section 10.3.2)																			
eDiary[4]	<- ========== ->																		
POEM and DLQI		X				X				X				X				X	
EQ-5D-5L and HADS		X				X				X				X				X	
SF-36 and WPAI-GH		X				X				X				X				X	
TSQM				X														X	
Safety assessments (Sections 10.4 and 11)																			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination								X								X		X	X
ECG				X				X				X				X		X	X
Urine pregnancy test		X		X		X		X		X		X		X		X		X	X

Panel 3 Schedule of trial procedures: maintenance treatment period and follow-up (continued)

	Maintenance treatment period																		FU1[2]
Visit	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30[1]**	**31**
Week	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**66**
Safety assessments (Sections 10.4 and 11)																			
Serum chemistry, haematology, and IgE		X		X		X		X		X		X		X		X		X	X
Urinalysis				X				X				X				X		X	X
Pharmacokinetics						X												X	X
ADA						X												X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other assessments (Section 10.5)																			
Skin swabs (S. aureus)																		X	
Skin swabs (microbiome)[5]																		X	
Serum biomarkers (small panel)						X												X	
Serum biomarkers (large panel)[5]						X												X	
Photography[5]		X		X		X		X		X		X		X		X		X	

1) Assessments also to be done at an early termination visit.

2) Subjects will have a safety follow-up (FU1) 16 weeks after last injection of IMP; this is considered the end of trial visit. For subjects who are enrolled into the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]), the end of trial visit will be the last visit in trial LP0162-1325 before transfer to the extension.

3) Subjects who meet the following criteria will be transferred to open-label treatment (tralokinumab 300 mg Q2W with optional use of TCS [Panel 4]):

- Subjects with IGA=0 at Week 16: IGA of at least 2 and not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits).
- Subjects with IGA=1 at Week 16: IGA of at least 3 and not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits).
- Subjects with IGA >1 at Week 16: not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits).

The first injections of open-label treatment will be given at the visit in the maintenance period where the subject meets these criteria.

4) The eDiary consists of (i) Eczema-related Sleep NRS, (ii) Worst Daily Pruritus NRS, (iii) Average Daily Pruritus NRS, (iv) PGI-B, and (v) PGI-S.
5) Optional, selected trial sites only.

ADA, anti-drug antibodies; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI50, at least 50% reduction in EASI score; EASI75, at least 75% reduction in EASI score; 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; PGI-B, Patient Global Impression of Bother; PGI-S, Patient Global Impression of Severity; POEM, Patient Oriented Eczema Measure; Q2W, every 2 weeks; SCORAD, Scoring Atopic Dermatitis; SF-36, 36-Item Short Form Health Survey; TCS, topical corticosteroids; TSQM, Treatment Satisfaction Questionnaire for Medication; WPAI-GH, Work Productivity and Activity Impairment – General Health.

Panel 4 Schedule of trial procedures: open-label tralokinumab and follow-up

	Open-label tralokinumab treatment																		FU1[2]
Visit	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30[1]**	**31**
Week	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**66**
Visit window (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Trial population and eligibility (Section 8 and Appendix 4B)																			
Informed consent (home-use)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Trial products (Section 9)																			
IMP administration and compliance	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4,5]	
Concomitant medications/procedures	X	X	X[6]	X	X[6]	X	X[6]	X	X[6]	X	X[6]	X	X[6]	X	X[6]	X	X[6]	X	X
Investigator assessments of efficacy (Section 10.3.1)																			
IGA		X		X		X		X		X		X		X		X		X	
EASI		X		X		X		X		X		X		X		X		X	
SCORAD		X		X		X		X		X		X		X		X		X	
Safety assessments (Sections 10.4 and 11)																			
Vital signs	X[4]	X[4]	X[4,6]	X[4]	X[4,6]	X[4]	X[4,6]	X[4]	X[4,6]	X[4]	X[4,6]	X[4]	X[4,6]	X[4]	X[4,6]	X[4]	X[4,6]	X	X
Physical examination								X								X		X	X
ECG				X				X				X				X		X	X
Urine pregnancy test		X		X		X		X		X		X		X		X		X	X
Serum chemistry, haematology, and IgE		X		X		X		X		X		X		X		X		X	X
Urinalysis				X				X				X				X		X	X
Pharmacokinetics						X												X	X
ADA						X												X	X

Panel 4 Schedule of trial procedures: open-label tralokinumab and follow-up (continued)

	Open-label tralokinumab treatment																		FU1[2]
Visit	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30[1]**	**31**
Week	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**66**
Safety assessments (Sections 10.4 and 11)																			
Adverse events	X	X	X[6]	X	X[6]	X	X[6]	X	X[6]	X	X[6]	X	X[6]	X	X[6]	X	X[6]	X	X
Other assessments (Section 10.5)																			
Skin swabs (S. aureus)																		X	
Skin swabs (microbiome)[7]																		X	
Serum biomarkers (small panel)						X												X	
Serum biomarkers (large panel)[7]						X												X	
Photography[7]		X		X		X		X		X		X		X		X		X	

1) Assessments also to be done at an early termination visit.
2) All subjects will have a safety follow-up (FU1) 16 weeks after last injection of IMP, except subjects who are enrolled into the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]) after completion of the treatment periods.
3) Subjects who are eligible for home-use during open-label treatment will have to provide additional informed consent before the training at the site (Section 9.2); home-use will only commence after proper training of the subject or caregiver (at 3 dosing visits after the additional consent has been obtained) and after 3 doses of open-label tralokinumab administered at the trial site, i.e., starting no earlier than Week 22, depending on when the subject transfers to open-label treatment (selected countries only).
4) For the first 3 IMP dosing visits in the open-label treatment period, subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later (Section 9.2).
5) IMP administration at Week 52 only applicable for subjects who continue into the short-term extension of the trial (selected countries only; see Panel 5).
6) Not applicable for subjects self-administering tralokinumab (home-use; selected countries only; Sections 7.1 and 9.2).
7) Optional, selected trial sites only.

ADA, anti-drug antibodies; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; IGA, Investigator's Global Assessment; IgE, immunoglobulin E; IMP, investigational medicinal product; SCORAD, Scoring Atopic Dermatitis.

Panel 5 Schedule of trial procedures: short-term extension and follow-up (selected countries)

	Open-label short-term extension[1]								FU2[3]
Visit	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38[2]**	**39**
Week	**54**	**56**	**58**	**60**	**62**	**64**	**66**	**68**	**82**
Visit window (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3
Trial products (Section 9)									
IMP administration and compliance	X	X	X	X	X	X	X		
Concomitant medications/procedures	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X
Investigator assessments of efficacy (Section 10.3.1)									
IGA		X		X		X		X	
EASI		X		X		X		X	
SCORAD		X		X		X		X	
Safety assessments (Sections 10.4 and 11)									
Vital signs	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X
Physical examination								X	X
ECG				X				X	X
Urine pregnancy test		X		X		X		X	X
Serum chemistry, haematology, and IgE		X		X		X		X	X
Urinalysis		X				X		X	X
Pharmacokinetics								X	X
ADA								X	X
Adverse events	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X

1) Only subjects who join the open-label tralokinumab arm at Week 16.
2) Assessments to be done at an early termination visit.
3) All subjects will have a safety follow-up (FU2) 16 weeks after last administration of IMP. This is considered the end of trial visit.
4) Not applicable for subjects self-administering tralokinumab (home-use; selected countries only; Sections 7.1 and 9.2).

ADA, anti-drug antibodies; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; IGA, Investigator's Global Assessment; IgE, immunoglobulin E; IMP, investigational medicinal product; SCORAD, Scoring Atopic Dermatitis.

5 Introduction and 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 enhanced 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, sleep disturbance, and reductions in work productivity (5).

Treatment recommendations for AD include topical therapies, the main being topical corticosteroids (TCS). Unfortunately, TCS and topical calcineurin inhibitors (TCIs) have limited efficacy in patients with moderate-to-severe disease. TCS and non-biologic systemic therapies are all associated with toxicities with long-term use (6-8).

AD is characterised by an activated T-helper-2 (Th2) pathway with increased skin expression of key Th2 cytokines including interleukin (IL)-13 (9, 10). 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 (9, 11).

IL-13 acts on keratinocytes to release C-C motif chemokine 22 (CCL22) and recruit more IL-13 expressing Th2 cells, decrease differentiation, and contribute to decreased barrier function (12). 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 (13, 14). Indeed, itch is a key issue in AD, which drives significant mechanical damage to the skin and further facilitates allergen and pathogen entry.

All of 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 which also binds IL-13) with the monoclonal antibody dupilumab leads to clinical improvement in AD subjects (15).

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 (16-18). A compilation of clinical and nonclinical data on tralokinumab including pharmacokinetics (PK) is given in the current Investigator's Brochure.

In total, 17 clinical trials have been conducted with tralokinumab, with phase 3 development ongoing in asthma and AD. Other clinical trials with tralokinumab have been conducted in subjects with ulcerative colitis, idiopathic pulmonary fibrosis, and in healthy subjects. Further information on these trials can be found in the current Investigator's Brochure.

In a phase 2b trial (D2213C00001), adults with moderate-to-severe AD on a background of mild to moderate TCS, were treated with 3 different regimens of tralokinumab (45 mg every second week [Q2W], 150 mg Q2W, or 300 mg Q2W) or placebo to evaluate the safety and efficacy over a treatment period of 12 weeks. The primary endpoints were change from baseline in Eczema Area and Severity Index (EASI) at Week 12 and the percentage of subjects achieving 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, 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 was upper respiratory tract infection (6 [3.9%] subjects in the combined tralokinumab group (45 mg, 150 mg, and 300 mg) and 2 [3.9%] subjects in the placebo group).

In total, more than 2,343 subjects have been treated with tralokinumab (cut-off date: 18-Aug-2017) based on actual exposure data from any completed clinical trials and the enrolment/randomisation schemes for ongoing trials. The safety of all doses studied so far has been with an acceptable benefit-risk profile and no major safety concerns have been identified. Possible risks associated with use of tralokinumab are summarised in Section 5.5.

5.3 Trial rationale

The purpose of this phase 3 trial is to provide evidence of the efficacy and safety of tralokinumab monotherapy in the treatment of subjects with moderate-to-severe AD inadequately controlled with topical therapies. Such subjects would be candidates for systemic therapy.

The primary objective of this trial is to demonstrate that tralokinumab provides more effective control of the skin manifestations of AD than placebo. The trial will evaluate the percentage of subjects achieving IGA response of 0 (clear) or 1 (almost clear) and the percentage of subjects achieving at least 75% reduction in EASI score (EASI75) at Week 16, with

secondary endpoints addressing symptom scores and extent of AD (SCORAD), itch severity, and health-related quality of life (HQoL) measures related to AD.

As AD is a chronic disease requiring long-term treatment, it is also relevant to evaluate the efficacy of tralokinumab as maintenance treatment. After the 16-week initial treatment period, the trial will evaluate 2 different treatment options for maintenance therapy (300 mg Q2W and 300 mg every 4 weeks [Q4W]).

As an exploratory component, the present trial will also investigate whether subjects who have elevated levels of biomarkers of IL-13 may be more likely to respond to an IL-13 neutralising therapy. Periostin and dipeptidyl peptidase 4 (DPP4) were identified as key markers of IL-13 mediated activation in the phase 2b trial (D2213C00001). In a post-hoc analysis of trial D2213C00001, subjects with baseline serum DPP4 or periostin levels above the median were seen to derive greater benefit from tralokinumab. Further exploratory analyses of these biomarkers will be conducted so as to identify sub-populations where prospective testing may be conducted in future clinical trials.

The trial will further characterise the benefit-risk profile of the drug and understand how best to position tralokinumab in the AD treatment pathway.

5.4 Justification for dose

The selected dose for the initial treatment period in trial is subcutaneously administered 300 mg tralokinumab Q2W. All subjects randomised to receive 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 support 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 this trial.

In the maintenance treatment period, 1 of the treatment arms will be dosed with tralokinumab Q4W. This approach will allow the sponsor of the trial, LEO Pharma A/S (hereinafter "LEO"), to establish whether less frequent dosing of tralokinumab may be sufficient for long-term maintenance of efficacy.

5.5 Benefit/risk assessment

There is an unmet medical need for new therapies for use in subjects with moderate-to-severe AD as current immunosuppressive medications, such as cyclosporine, methotrexate, and azathioprine, have associated long-term toxicities.

Tralokinumab has already demonstrated efficacy in both moderate-to-severe AD as well as in a severe asthma population in phase 2 trials, and has shown an acceptable safety profile in AD, asthma, ulcerative colitis, idiopathic pulmonary fibrosis, and in trials with healthy subjects. The evidence discussed in Section 5.2 further supports the hypothesis that tralokinumab may benefit individuals with AD.

In clinical trials completed to date tralokinumab was well tolerated. A number of theoretical potential risks have been identified that are described in the current 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 SoP (Section 4). Where home-use is appropriate (open-label treatment only), trial visits will be scheduled every 4 weeks.
- Close monitoring of subjects during the post-dosing period (at the first 3 investigational medicinal product [IMP] dosing visits in initial treatment period and in open-label treatment) as a precautionary measure against hypersensitivity reactions (further details are given in Section 9.2).

- Monitoring of subjects for both 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) [29])
- 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 anti-fungal 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 risk/benefit ratio is favourable and supports the administration of tralokinumab for the purposes of achieving the objectives of this trial.

5.6 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 have to agree to use a highly effective method of contraception to prevent pregnancy during the clinical trial and until 16 weeks after discontinuation of treatment with the IMP. In addition, all female subjects of 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 this clinical trial, the efficacy of tralokinumab will be evaluated in adult subjects with moderate-to-severe AD who are otherwise healthy. Tralokinumab treatment will be compared with a placebo control group. Subjects who do not achieve a clinical response (IGA 0/1 or EASI75) at Week 16 will be transferred to open-label tralokinumab 300 mg Q2W treatment with optional use of TCS. Similarly, during the maintenance treatment period, subjects who

meet the protocol definition of transfer to open-label will be treated with open-label tralokinumab 300 mg Q2W with optional use of TCS.

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 moderate-to-severe AD. Moreover, 75% of the subjects will be randomised to active treatment with tralokinumab in the initial treatment phase and those who do not achieve a clinical response at Week 16 (including subjects randomised to placebo) will be treated with open-label tralokinumab in the maintenance phase with a potential effect and benefit for the individual subject.

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. Safety data will be reviewed regularly by Global Pharmacovigilance, LEO and an independent Data Monitoring Committee (DMC; see Appendix 4H) to ensure that prompt action is taken, if needed, to maximise patient safety.

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

6 Trial objectives and endpoints

The initial treatment period (randomisation until Week 16) will be analysed separately from the maintenance treatment period (Week 16 until Week 52; subjects who responded and were re-randomised at Week 16). For this reason, the objectives and endpoints for the 2 treatment periods are listed separately in Panel 6 and Panel 7.

6.1 Initial treatment period of Weeks 0 to 16

Panel 6 Objectives and endpoints: initial treatment period

Objectives	Endpoints
Primary objective	Primary endpoints
To evaluate the efficacy of tralokinumab compared with placebo in treating moderate-to-severe AD.	• IGA score of 0 (clear) or 1 (almost clear) at Week 16 • EASI75 at Week 16
Secondary objectives	Secondary endpoints
To evaluate the efficacy of tralokinumab on severity and extent of AD, itch, and health related quality of life compared with placebo.	*Severity and extent of AD* • Change in SCORAD from baseline to Week 16 *Itch* • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to Week 16 *Quality of life* • Change in DLQI score from baseline to Week 16
Additional secondary objectives	Additional secondary endpoints
To evaluate the safety and tolerability of tralokinumab when used to treat moderate-to-severe AD for 16 weeks. To support the primary and secondary objectives in the trial.	*Safety and tolerability* • AE/SAE frequency by preferred term • Frequency of anti-drug antibodies *Supporting primary endpoints* • EASI50 at Week 16 • EASI90 at Week 16 • Change from baseline to Week 16 in EASI score *Supporting severity and extent of AD* • SCORAD75 at Week 16 • SCORAD50 at Week 16 *Supporting itch* • Change from baseline to Week 16 in Worst Daily Pruritus NRS (weekly average) • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 3 from baseline to Week 16 *Supporting quality of life* • Reduction from baseline to Week 16 of DLQI of ≥4 points among subjects with baseline DLQI ≥4

Panel 6 Objectives and endpoints: initial treatment period (continued)

Objectives	Endpoints
Other objectives	Other endpoints
To evaluate the efficacy over time of tralokinumab on severity and extent of AD, itch, and health-related quality of life compared with placebo.	• IGA 0/1 at each scheduled assessment until Week 14 • EASI75 at each scheduled assessment until Week 14 • Change in SCORAD from baseline to each scheduled assessment until Week 14 • Change from baseline to each week through Week 1 to 15 in Worst Daily Pruritus NRS (weekly average) • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to each week through Week 1 to 15 • Change in DLQI score from baseline to each scheduled assessment until Week 14
To evaluate the efficacy of tralokinumab compared with placebo on patient-reported outcomes and health care resource utilisation.	• Reduction of Worst Daily Pruritus NRS (weekly average) of at least 3 from baseline to Week 2 • Change from baseline to Week 16 in Eczema-related Sleep NRS weekly average • Change from baseline to Week 16 in HADS • HADS anxiety and HADS depression scores <8 at Week 16 in subjects with baseline HADS anxiety or HADS depression subscale scores of ≥8 • Change from baseline to Week 16 in POEM • Reduction from baseline to Week 16 of POEM of ≥4 points among subjects with baseline POEM ≥4 • Change from baseline to Week 16 in SF-36 • Change from baseline to Week 16 in EQ-5D-5L • Change from baseline to Week 16 in WPAI-GH • Treatment satisfaction (TSQM) at Week 16
To evaluate the incidence of skin colonisation with Staphylococcus aureus in tralokinumab treated patients compared with placebo at Week 16.	• Skin colonisation of S. aureus at Week 16 among subjects who are positive at baseline

AD, atopic dermatitis; AE, adverse event; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI50, at least 50% reduction in EASI score; EASI75, at least 75% reduction in EASI score; EASI90, at least 90% reduction in EASI score; 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; SAE, serious adverse event; SCORAD, Scoring Atopic Dermatitis; SCORAD50, at least 50% reduction in SCORAD score; SCORAD75, at least 75% reduction in

SCORAD score; SF-36, 36-Item Short Form Health Survey; TSQM, Treatment Satisfaction Questionnaire for Medication; WPAI-GH, Work Productivity and Activity Impairment – General Health.

6.2 Maintenance treatment period of Weeks 16 to 52 for responders at Week 16

Panel 7 Objectives and endpoints: maintenance treatment period

Objectives	Endpoints
Maintenance objective	Maintenance endpoints
To evaluate maintenance of effect with continued tralokinumab dosing up to 52 weeks compared to placebo for subjects achieving clinical response at Week 16.	• IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab • EASI75 at Week 52 among subjects with EASI75 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab
Other maintenance objectives	Other maintenance endpoints
To evaluate the safety and tolerability of tralokinumab when used to treat moderate-to-severe AD for 52 weeks.	• AE/SAE frequency by preferred term • Frequency of anti-drug antibodies
To evaluate time to relapse in the maintenance treatment period.	• Time to relapse applying IGA of 0/1 • Time to relapse applying EASI75
To evaluate the efficacy of maintenance treatment up to Week 52 among subjects randomised to the maintenance treatment period with EASI75 and IGA≥2 at Week 16.	• IGA of 0/1 at Week 52 among subjects with EASI75 and IGA≥2 at Week 16
To support the maintenance objective in the trial.	• IGA 0/1 or EASI75 at Week 52 among subjects with IGA 0/1 or EASI75 at Week 16 achieved without rescue medication

AD, atopic dermatitis; AE, adverse event; EASI75, at least 75% reduction in Eczema Area and Severity Index score; IGA, Investigator's Global Assessment; SAE, serious adverse event.

The maintenance endpoints of IGA 0/1 and EASI75 at Week 52 for subjects achieving clinical response at Week 16 without rescue medication are considered secondary endpoints. The additional maintenance endpoints are considered other endpoints. In Japan, the maintenance endpoints of IGA 0/1 and EASI75 at Week 52 for subjects achieving clinical response at Week 16 without rescue medication are evaluated as primary maintenance endpoints. This regulatory requirement will have no impact on the analysis since an adjustment for multiplicity is implemented for these 2 endpoints (Panel 15).

7 Trial design

7.1 Overall trial design

Overview

This is a phase 3 randomised, double-blinded, placebo-controlled trial in adult subjects with moderate-to-severe AD. The trial will consist of a screening period of 2 to 6 weeks (Weeks -6/-2 to 0), an initial treatment period of 16 weeks (Weeks 0 to 16) and a maintenance treatment period of 36 weeks (Weeks 16 to 52). The primary endpoint is assessed at Week 16, and the final efficacy assessment will be conducted at Week 52. A 14-week off-treatment follow-up period for the assessment of safety is also included (Weeks 52 to 66). Subjects not achieving a clinical response at Week 16 as well as those who meet certain criteria during maintenance treatment will be transferred to open-label tralokinumab 300 mg Q2W treatment with optional use of TCS up to Week 52. An overview of the different parts of the trial is provided in Panel 1 and Panel 9.

Screening period (Week -6 to Week 0)

The screening period has a minimum duration of 2 weeks and a maximum duration of 6 weeks and includes 1 or 2 screening visits. The exact duration of the screening period depends on the washout period defined by the exclusion criteria (Section 8.3). If a washout is not required, screening will be reduced to 2 weeks and only requires 1 visit (Week -2; visit 2), i.e., the 2 screening visits will be merged. Similarly, if only a 2-week wash-out is required, screening visits 1 and 2 will be combined (Week -2; visit 2). Eligibility will be assessed at the (first) screening visit and on Day 0 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 the eDiary. Data entered in 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. Subjects will initiate emollient treatment no later than the Week -2 visit.

Initial treatment period (Week 0 to Week 16)
Following the screening period, approximately 780 subjects will be randomised 3:1 to one of the following groups stratified by region and disease severity (IGA of 3 or 4)

- Tralokinumab 600 mg (4 mL) at Day 0 (hereinafter "baseline"), then 300 mg (2 mL) Q2W.
- Placebo (4 mL) at baseline, then placebo (2 mL) Q2W.

Maintenance treatment period (Week 16 to Week 52)
Subjects achieving a clinical response at Week 16 will continue into maintenance treatment that will continue until Week 52.

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

Subjects randomised to tralokinumab in the initial treatment period will be re-randomised 2:2:1 to one of the following Q2W maintenance regimens stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1):

- Tralokinumab 300 mg (2 mL) ('tralokinumab Q2W').
- Alternating dose administrations tralokinumab 300 mg (2 mL) and placebo (2 mL) ('tralokinumab Q4W').
- Placebo (2 mL).

Subjects randomised to placebo in the initial treatment period who achieve a clinical response at Week 16, defined by IGA of 0 or 1, or EASI75 will continue to receive placebo Q2W in the maintenance treatment period.

Transfer to open-label treatment
Subjects will be transferred from maintenance treatment to open-label treatment (tralokinumab 300 mg Q2W with optional use of TCS) if they meet the criteria listed below. Transfer to open-label may occur at any visit while the subject is in the maintenance treatment period but no earlier than Week 22.

Subjects with IGA=0 at Week 16:

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

Subjects with IGA=1 at Week 16:

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

Subjects with IGA >1 at Week 16:

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

Subjects who are transferred to open-label treatment will continue their scheduled visit sequence.

Open-label treatment (Week 16 to Week 52)
Any subject that does not achieve the protocol defined clinical response at Week 16 will be treated with open-label tralokinumab 300 mg Q2W with optional use of TCS. The open-label treatment will extend to Week 52.

For selected countries
Subjects transferring to open-label treatment will have the option to self-administer tralokinumab – or have tralokinumab administered by a caregiver – in their home after adequate training by site staff at the investigator's discretion (Section 9.2). This home-use will only commence after 3 doses of tralokinumab have been administered at the trial site (i.e., starting no earlier than Week 22, depending on when the subject transferred to open-label) as a safety precaution for subjects receiving their first active therapy. After proper training of the subject and/or the caregiver that is, at 3 or more dosing visits during open-label treatment after additional consent for home-use has been obtained, these subjects will only have trial visits every 4 weeks. For subjects where home-use is inappropriate, tralokinumab will continue to be administered by site staff at the trial visit.

Short-term extension (Week 52 to Week 68)
For selected countries
Subjects who join the open-label tralokinumab arm at Week 16 will continue an additional 16 weeks of open-label treatment in order to secure at least 52 weeks of active therapy.

Safety follow-up period (Week 52 to Week 66 [or Week 68 to Week 82])
All subjects, except for 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 and ADA at Week 66 (or Week 82).

Long-term extension trial
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 52 or Week 68 [*selected countries*]) under the current protocol (LP0162-1325).

7.2 Number of subjects needed

Assuming a screening failure rate of 25%, approximately 1040 subjects will be screened and approximately 780 subjects will be randomly assigned to trial treatment in the initial treatment period (3:1; 585 subjects in the tralokinumab arm and 195 subjects in the placebo arm). At Week 16, approximately 40% of the tralokinumab treated subjects are expected to be re-randomised (2:2:1 to tralokinumab Q2W, tralokinumab Q4W, and placebo, respectively) into the maintenance treatment period; any subject who does not achieve a clinical response at Week 16 will be treated with open-label tralokinumab Q2W.

The statistical power considerations for this sample size (n=780) are described in Section 12.1.

This trial will be conducted at approximately 130 sites in Europe, North America, and Japan. The anticipated minimum number of subjects per trial site is 4 and the maximum number of subjects 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 safety follow-up visit (FU1 [Week 66] or FU2 [Week 82]). Subjects entering the long-term extension trial (LP0162-1337, ECZTEND) after completion of the end of treatment visits (Week 52 or Week 68) 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.

8 Trial population and withdrawal

8.1 Subject eligibility

The investigator should only enrol 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 checked according to the inclusion and exclusion criteria at visits specified in Panel 2.

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

8.2 Inclusion criteria

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

2. Age 18 and above.

3. Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD (34; Appendix 5).

4. Diagnosis 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 or for whom topical treatments are otherwise medically inadvisable (e.g., due to important side effects or safety risks).

    - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=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.
- Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the subject's treating physician.

6. AD involvement of ≥10% body surface area at screening and baseline (visit 3).

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

8. An IGA score of ≥3 at screening and at baseline.

9. A Worst Daily Pruritus numeric rating scale (NRS) average score of ≥4 during the week prior to baseline.

    - Worst Daily Pruritus NRS 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 (refer to exclusion criterion no. 8 for limitations regarding emollients).

11. Women of childbearing 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).

8.3 Exclusion criteria

1. Concurrent enrolment in another clinical trial where the subject is receiving an IMP.
2. Previous randomisation in tralokinumab trials.
3. Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis.
4. Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD.
5. Use of tanning beds or phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]), within 6 weeks prior to randomisation.
6. Treatment with the following medications within 4 weeks prior to randomisation:
    - Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine, azathioprine, mycophenolate mofetil, Janus kinase inhibitors etc.).
    - Systemic corticosteroid use (excludes topical, inhaled, or intranasal delivery).
    - Three or more bleach baths during any week within the 4 weeks.
7. Treatment with the following medications within 2 weeks prior to randomisation
    - TCS.
    - TCI.
    - Topical PDE-4 inhibitor.

8. Initiation of treatment of AD with prescription emollients or emollients containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (subjects may continue using stable doses of such emollients if initiated before the screening visit).
9. Receipt of live attenuated vaccines 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) are allowed, provided they are not administered within 5 days before/after any study visit.
10. Receipt of any marketed (i.e. immunoglobulin, anti-IgE) or investigational biologic agent, including dupilumab:
    - Any cell-depleting agents including but not limited to rituximab: within 6 months prior to randomisation, or until lymphocyte count returns to normal, whichever is longer.
    - Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to randomisation.
11. 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 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 biologic 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 is 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 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.

8.4 Screening, screening failures, and randomisation

Trial participation begins once written informed consent is obtained (see Appendix 4B for details on the informed consent process). Once informed consent is obtained, a subject identification number (subject ID) will be assigned by a central interactive web response system (IWRS) 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. A master log of all consented subjects will be maintained at the trial site.

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 (27) and to respond to queries from regulatory authorities. Minimal information includes demography, screening failure details, eligibility criteria, and any adverse events (AEs) and serious AEs (SAEs). Follow-up of SAEs must be carried out according to Section 11.6.

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

The investigator will maintain a list of all randomised subjects at the trial site including each subject's identity, date of enrolment and corresponding subject ID so that any subject may be identified if required for any reason. The list must not be copied or retained by LEO.

Note that enrolment is defined as the period from screening to randomisation (i.e., subjects are not enrolled until randomised) (27).

8.5 Discontinuation

A subject may withdraw from trial or from treatment at any time (prior to first dose or during treatment period) at his/her own request. A subject may be withdrawn at any time at the discretion of the investigator. Discontinued subjects will not be replaced.

Medical reasons for permanent discontinuation of IMP are given in Section 9.8.1.

Assessments
Subjects who permanently discontinue IMP for any reason will be asked to attend an early termination visit and return to the trial site for 1 or 2 additional visits as indicated below depending on the time of discontinuation of IMP (see the SoP [Section 4] for data to be collected at these visits). The investigator will review any AEs which will be followed-up according to Section 11.6, if the subject agrees.

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

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

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

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

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site's trial records.

Reason(s) for discontinuation from IMP and withdrawal from the trial must be recorded in the medical records and the eCRF (lack of efficacy, AE, withdrawal by subject, lost to follow-up, death, other). For subjects randomised to IMP but not attending any post-baseline visits, it will be recorded whether any safety evaluations were performed after exposure to IMP.

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 and/or should 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.

9 Treatments

9.1 Trial product description

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

Tralokinumab and placebo will be packaged in individually numbered kits, each containing 1 syringe. Refer to Panel 8 for further details.

Panel 8 Identification of investigational medicinal products

Investigational medicinal product	Dosage form	Concentration and formulation	Manufacturer
Tralokinumab	150 mg/mL solution for injection in an accessorised pre-filled syringe, 1.0 mL fill volume.	Formulated at a nominal concentration of 150 mg/mL in 50mM sodium acetate/acetic acid buffer, 85mM sodium chloride, 0.01% (w/v) PS-80, pH 5.5 solution.	MedImmune
Placebo	Placebo solution for injection in an accessorised pre-filled syringe, 1.0 mL fill volume.	Placebo contains the same excipients, in the same concentration only lacking tralokinumab	MedImmune

The accessorised prefilled 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 prefilled syringe consists of a prefilled syringe sub-assembly (1 mL prefilled syringe barrel with a 1/2 inch 27 gauge thin wall staked in needle, rigid needle shield, plunger stopper) and a safety device.

No active comparators will be used in this trial.

9.2 Administration of investigational medical products

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

The first day of dosing is considered Day 0 (visit 3). Each subject will receive 4 SC injections (each 1.0 mL) of 150 mg tralokinumab or placebo to receive a total loading dose of 600 mg tralokinumab or placebo (4.0 mL).

At subsequent visits (Q2W) in the initial treatment period, each subject will receive 2 SC injections (each 1.0 mL) of 150 mg tralokinumab or placebo to receive a total dose of 300 mg tralokinumab or placebo.

Subjects in the maintenance period will receive either

- Tralokinumab Q2W (2 SC injections [each 1.0 mL] of 150 mg tralokinumab).
- Tralokinumab Q4W (alternating dose administrations 2 SC injections [each 1.0 mL] of 150 mg tralokinumab and placebo).
- Placebo (2 SC injections [each 1.0 mL] of placebo).

Subjects who have been transferred to open-label treatment will receive 2 SC injections (each 1.0 mL) of 150 mg tralokinumab at each dosing interval.

Dosing visits are shown in the SoP (Section 4). The last administration of IMP under this protocol will occur at Week 50 (or Week 66).

IMP will be administered by a qualified, unblinded healthcare professional (HCP; see Section 9.3.1 for blinding details), or by the subject or the subject's caregiver (open-label treatment only; selected countries). A minimum interval of 7 days is required between 2 dosing visits.

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

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

After IMP administration

For the first 3 IMP dosing visits in both the initial treatment period (i.e., Weeks 0, 2, and 4) and in open-label treatment, subjects will be monitored after IMP administration for

immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later. Vital signs will be documented in the eCRF.

As with any antibody, allergic reactions to dose administration are possible. The World Allergy Organization has categorised anaphylaxis into 2 subgroups: allergic anaphylaxis (mediated by an immunologic mechanism) and nonallergic anaphylaxis (which has a nonimmunologic cause) (31). The clinical criteria for defining anaphylaxis for this trial are listed in Appendix 6 (35). Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc., and medical equipment to treat acute anaphylactic reactions must be immediately available at 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 IMP administration rescheduling
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; ≥100.4°F) within 72 hours prior to IMP administration.

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

Home-use
Subjects transferring to open-label treatment will have the option to self-administer tralokinumab – or have tralokinumab administered by a caregiver – in their home after training and at the investigator's discretion (selected countries only). Subjects who do not want to self-inject may have the staff at the trial site administer all the injections at the trial site.

Subjects who are found eligible for home-use will have to provide additional informed consent and home-use will only commence after 3 doses of tralokinumab have been administered at the trial site (i.e., starting no earlier than Week 22, see Section 7.1 and the SoP

[Panel 4]). Home-use will start no later than Week 50 (this also applies for subjects in the short-term extension).

Prior to self-administration at home, the individual who will be administering the injections (i.e., the subject and/or the caregiver) will receive proper training (that is, at 3 dosing visits during open-label treatment after additional consent has been obtained) in SC injection technique and on procedures to be followed in the event of an emergency during or following home-use of tralokinumab. This training will be conducted by the unblinded HCP.

The subject and/or the caregiver must also undertake SC administration under HCP supervision on one or more occasions such that the HCP is satisfied with the individual's understanding and confidence of the procedure.

Subjects or their caregivers will only self-administer tralokinumab at home every 4 weeks, i.e., in weeks where no efficacy and safety assessments are scheduled (Panel 4 and Panel 5; see also Section 9.9.3). Where trial visits with efficacy and safety assessments are scheduled (every 4 weeks), tralokinumab injections will be administered at the trial site, preferably by the subject or their caregiver, alternatively by the unblinded HCP, when all assessments have been completed.

At each trial visit it will be recorded in the eCRF whether tralokinumab was administered by the subject or the unblinded HCP.

9.3 Treatment assignment

Subjects who have been found to comply with all the inclusion criteria and not to violate any of the exclusion criteria will be randomised at baseline (Day 0) to receive treatment with either tralokinumab or placebo in the initial treatment period. Treatment assignment will be pre-planned according to a computer-generated randomisation schedule in a 3:1 ratio (tralokinumab:placebo) stratified by region (North America, Japan, and Europe) and baseline disease severity (IGA 3 or 4).

Subjects found to be eligible for maintenance treatment at Week 16 will be re-randomised to the maintenance treatment period in a 2:2:1 ratio (tralokinumab Q2W:tralokinumab Q4W:placebo) stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1).

Subjects randomised to placebo in the initial treatment period who achieve a clinical response at Week 16 (IGA 0/1 or EASI75) will continue to receive placebo Q2W in the maintenance treatment period.

Subjects not eligible for the maintenance part of the trial will be transferred to open-label tralokinumab Q2W treatment.

IWRS will be used to control randomisation and stratification factors, along with IMP supply chain and expiry tracking.

9.3.1 Blinding

This is a double-blinded trial in which tralokinumab and placebo are visually distinct from each other. Neither the subject nor any of the investigator or LEO staff who are involved in the treatment or clinical evaluation and monitoring of the subjects will be aware of the treatment received. The packaging and labelling of the IMPs will contain no evidence of their identity.

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

In the event that the treatment allocation for a subject becomes known to the investigator or other study 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.

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

IWRS. For a requester who is not a member of the trial staff and who does not have access to the IWRS (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 4B) 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 provide the requester with the LEO 24/7 contact which will be diverted to the medical cover.

9.4 Background treatment (emollients)

All subjects must use an additive-free, basic bland emollient twice daily (or more, as needed) for at least 14 days before randomisation. Subjects are not allowed to start treatment with prescription emollients or emollients containing additives such as ceramide, hyaluronic acid, urea, or filaggrin, unless initiated prior to the screening visit (Section 9.6). Subjects must continue their background emollient treatment throughout the trial.

9.5 Concomitant medication and procedures

Any medication or vaccine that the subject receives from 3 months prior to screening through safety follow-up (FU1 [Week 66] or FU2 [Week 82]) must be recorded in the subject's medical record and the eCRF along with details such as:

- Reason for use.
- Dates of administration including start and stop dates.
- Dosage information including dose and frequency.
- For topical treatments: size of treated area (≤250 cm2 or >250 cm2).

Similarly, concomitant procedures (including body location, diagnosis, and start and stop date) must also be recorded in the subject's medical record and the eCRF. Note: in this trial, only surgical procedures will be recorded.

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 9.6. The

sponsor's medical expert should be contacted if there are any questions regarding concomitant or prior therapy.

Concomitant medication for conditions other than AD may be continued throughout the trial without any change in dosage whenever possible.

The following concomitant medications related to AD treatment are permitted from screening through safety follow-up (FU1 [Week 66] or FU2 [Week 82]):

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

In addition, the use of topical treatments is permitted during safety follow-up (from Week 52 or Week 68) at the investigator's discretion.

9.6 Prohibited medication and procedures

The following medications are prohibited during the trial from randomisation through Week 52 (or Week 68):

- TCS of any WHO class (except for subjects in open-label treatment).
- Other topical medications used for the treatment of AD, such as TCI.
- Use of ultraviolet A or B (UVA or UVB), psoralen + UVA (PUVA), other phototherapy, or tanning beds.
- Prescription emollients or emollients containing additives such as ceramide, hyaluronic acid, urea, or filaggrin (unless treatment was initiated prior to screening).
- Three or more bleach baths per week.

Any prohibited topical treatments must be recorded as concomitant medication.

The following medications are prohibited during the trial from randomisation through safety follow-up (FU1 [Week 66] or FU2 [Week 82]):

- Investigational agents other than tralokinumab

- Immunoglobulin or blood products
- Systemic corticosteroids (nasal and inhaled corticosteroids are allowed)
- Systemic treatment for AD with an immunosuppressive/ immunomodulating agent (e.g., cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, Janus kinase inhibitors, interferon-gamma, or other biologics)
- Allergen immunotherapy
- Live (attenuated) vaccine

The sponsor's medical expert must be notified if a subject receives any of these medications during the trial.

9.7 Rescue treatment

Initial treatment period and maintenance treatment period
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. For the purpose of efficacy analysis, subjects who receive rescue treatment during the initial treatment period will be considered as non-responders, but they will continue IMP treatment if rescue consisted of topical medications.

TCI may be used for rescue, but should be reserved for problem areas only, for example face, neck, intertriginous and genital areas, etc. If possible, investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for subjects who do not respond adequately after at least 14 days of topical treatment.

If a subject receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.), IMP will be immediately discontinued (see Section 9.8.2, reasons for temporary discontinuation of IMP). After the treatment with these medications is completed, IMP may be resumed if deemed appropriate by the investigator and sponsor's medical expert, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

Investigators should make every attempt to conduct efficacy and safety assessments (for example disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose, if necessary.

Open-label tralokinumab arm only
From Week 16 through safety follow-up (FU1 [Week 66] or FU2 [Week 82]) subjects may use mild to moderate strength TCS and/or TCI as needed (prn usage) on lesional skin at the investigator's discretion (see Appendix 9 for TCS classification and examples). Use of TCS and TCI should be recorded as concomitant medication.

9.8 Dose modification and IMP discontinuation rules

9.8.1 Reasons for permanent discontinuation of IMP

Subjects will be permanently discontinued from 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 >3x ULN with total bilirubin >2x ULN (unless elevated bilirubin is related to Gilbert-Meulengracht Syndrome)
    - Confirmed AST and/or ALT >5x ULN (for more than 2 weeks)

Subjects in open-label treatment (tralokinumab 300 mg Q2W with optional use of TCS) who in the opinion of the subject or investigator have unacceptable treatment effect of tralokinumab may discontinue open-label treatment and enter the safety follow-up period.

9.8.2 Reasons for temporary discontinuation of IMP

IMP dosing may be temporarily suspended in the event of:

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

IMP dosing may resume after the medication leading to suspension of IMP is discontinued.

A decision to discontinue IMP temporarily or to reinstitute IMP treatment must be discussed with sponsor's medical expert. However, the investigator may suspend trial treatment at any time, even without consultation with sponsor's medical expert if the urgency of the situation requires immediate action and if this is determined to be in the subject's best interest. In such cases, sponsor's medical expert should be informed as soon as possible.

9.9 Treatment logistics and accountability

9.9.1 Labelling and packaging of IMPs

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. The inner label will be in English for kits used at trial sites.

9.9.2 Storage of IMPs

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

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

Storage of IMP may be delegated, e.g. to a hospital pharmacy, as locally applicable.

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

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

Damaged IMP should be documented via IWRS (refer to the IWRS manual for further details). Damaged IMP should not be used.

9.9.3 Drug accountability

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

An inventory (trial medication inventory log) must be kept of the IMP administered to each subject randomised in the trial. The trial medication inventory log must be available for inspection during monitoring visits and will be checked by the CRA to ensure correct dispensing of the IMP.

Full drug accountability will also be performed in the IWRS.

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

Trial sites which do not have such IMP destruction procedures in place will dispose used syringes in sharps bins which will be shipped to the contract manufacturing organisation (CMO).

The trial site will maintain trial kit cartons from used kits until reconciliation. The IMP must be fully accounted for by the CRA with the help of the unblinded HCP. Accountability must

be documented on the trial medication inventory log and in the IWRS. Following reconciliation, the trial kit cartons from used kits may be discarded.

All unused IMP supplied by the CMO on behalf of LEO will be returned to the CMO. IMP may be returned from the trial site either to the CMO directly or via the LEO Pharma A/S affiliate or CRO responsible for the running of the clinical trial. The IMP returned to the CMO will be reconciled with the individual drug accountability forms.

For more information about IMP accountability, please refer to the IMP manual.

Where home-use is appropriate, the following apply:

- Subjects will only attend trial visits every 4 weeks, i.e., in weeks where efficacy and safety assessments are scheduled (Section 9.2). At these trial visits, subjects will be provided with IMP to be administered at home at the next dosing interval.
- Subjects will be provided with sharps bins for used syringes. Filled sharps bins will be returned to the trial site.
- Subjects will return trial kit cartons, and any unused IMP at each trial visit.
- Unused IMP returned by the subjects to the trial site can be stored at room temperature and must be stored separately from non-allocated IMP.
- The trial medication inventory log will document all IMP handed out to and returned by each subject.

9.9.4 Trial product destruction

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

9.9.5 Treatment compliance

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

Where home-use is appropriate, the following apply:
Subjects will record date and injection site for each administration in a log of drug administration; these data will then be transcribed into the eCRF by site staff at the next trial visit. If a subject is found to be non-compliant, the investigator should remind the subject of

the importance of following the treatment instructions including taking the IMP as prescribed. Any non-compliance and the reason for it must be recorded in the eCRF.

Where tralokinumab is administered by the subject at the trial site (Section 9.2), the site staff will record compliance data in the eCRF.

9.10 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.

9.11 Reporting product complaints

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

Critical complaints (defined as any issue, defect, 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 Pharmacovigilance, 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 11.2 and 11.3.

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

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

Global Pharmacovigilance, LEO contact information for reporting product complaints:

Fax number: +45 7226 3287

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

10 Trial schedule and assessments

10.1 Overview

Evaluations to be done at each visit are shown in the schedule of procedures (SoP) in Section 4. Links to the relevant SoPs are given in Panel 9. Refer to Section 7.1 for further details on the trial design.

Panel 9 Overview of schedules of procedures

Period	Start	Stop	Follow-up visit	SoP
Screening and initial treatment	Week -6[1]	Week 16	Not applicable	Panel 2
Maintenance treatment[2]	Week 16	Week 52	Week 66	Panel 3
Open-label treatment[3]	Week 16	Week 52	Week 66	Panel 4
Selected countries only: short-term extension[4]	Week 52	Week 68	Week 82	Panel 5

1. For subjects who do not require a wash-out, screening will start at Week -2 (Section 7.1).
2. Subjects achieving a clinical response at Week 16 will continue into maintenance treatment that will continue until Week 52 (Section 7.1).
3. Any subject that does not achieve a clinical response at Week 16 will be treated with open-label tralokinumab 300 mg Q2W with optional use of TCS. In addition, subjects who meet certain criteria during maintenance treatment will also be transferred to open-label treatment (Section 7.1).
4. Subjects who transfer to open-label tralokinumab treatment at Week 16 will continue an additional 16 weeks of open-label treatment in order to secure at least 52 weeks active therapy (Section 7.1).

Q2W, every 2 weeks; SoP, schedule of procedures; TCS, topical corticosteroids.

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

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

- PROs.
- Investigator assessments (performed only by adequately trained investigators; the same investigator should perform all the evaluations for a given subject throughout the entire trial period) in the following order:
    1. SCORAD component C, then component A and B.
    2. IGA.
    3. EASI.
- Safety and laboratory assessments.

- Other assessments (skin microbiology, serum biomarkers, skin biopsies, photographs).
- Administration of IMP.

Subjects participating in the trial will be under careful supervision of a dermatologist or allergist. Investigators must be experienced in treating AD and have documented experience 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. The investigators performing the assessments must not be involved in the administration of IMP (Section 9.3.1).

10.2 Assessments performed only at screening/baseline

Assessments performed only at the screening and/or baseline visit include: assessment of eligibility criteria (including review of scores on the Columbia-Suicide Severity Rating Scale [C-SSRS] Screening version), demographics, medical history, height and weight, and body surface area (BSA) affected by AD. These are described in further detail below. Laboratory tests include hepatitis B, hepatitis C, HIV-1, HIV-2, and serum pregnancy test (Sections 10.4.4 and 10.4.5).

10.2.1 Columbia-Suicide Severity Rating Scale

The C-SSRS Screening version is a rater-administered instrument used to assess severity of suicidal ideation and suicidal behaviour through a series of simple, plain-language questions (36). The C-SSRS must be completed at screening to check that exclusion criterion no. 24 does not apply.

10.2.2 Demographics

The following demographic data will be recorded:

- Month and year of birth
- Sex
- Race: American Indian or Alaska Native, Asian (Japanese), Asian (others), Black or African American, Native Hawaiian or Other Pacific Islander, White, Other
- Ethnic origin (self-reported by the subject): Hispanic or Latino, not Hispanic or Latino

10.2.3 Medical history

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

- Skin disease history: all past and current skin disease history including:
    - Alopecia
    - Vitiligo
    - Herpes simplex
- 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.

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

10.2.4 Height and weight

The subject's height must be measured (without shoes) and weight must be determined (in indoor clothing and without shoes).

10.2.5 Body surface area involvement

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

10.3 Efficacy assessments

10.3.1 Investigator assessments

10.3.1.1 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 10). The IGA score will be assessed according to the SoP (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. Whenever possible, the IGA should be assessed by the same investigator at each visit to reduce inter-rater variability.

Panel 10 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).

10.3.1.2 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 (19). The EASI score will be assessed according to the SoP (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. Whenever possible, the EASI should be assessed by the same investigator at each visit to reduce inter-rater variability.

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

Panel 11 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)

AS, area score; EASI, Eczema Area and Severity Index; SS, severity score. Modified from (28).

Panel 12 EASI severity score scale and area score scale

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

Half-points (0.5; 1.5; 2.5) may also be used.

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

EASI, Eczema Area and Severity Index.

10.3.1.3 Scoring Atopic Dermatitis

The SCORAD is a validated tool to evaluate the extent and severity of AD lesions, along with subjective symptoms (20). The maximum total score is 103, with higher values indicating more severe disease. SCORAD will be assessed according to the SoP (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, edema/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

10.3.2 Subject assessments

10.3.2.1 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 52. The Eczema-related Sleep NRS is included in the investigator trial file.

10.3.2.2 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 52. The Worst Daily Pruritus NRS is included in the investigator trial file.

10.3.2.3 Average Daily Pruritus numeric rating scale

Subjects will assess their average itch over the past 24 hours using an 11-point NRS ('Average Daily Pruritus NRS') with 0 indicating 'no itch' and 10 indicating 'worst itch imaginable'. Subjects will complete the Average Daily Pruritus NRS as part of an eDiary each day in the morning from Week -2 (visit 2) until Week 52. The Average Pruritus NRS is included in the investigator trial file.

10.3.2.4 Patient Global Impression of Bother

The Patient Global Impression of Bother (PGI-B) is a single item designed to capture the subject's perception of how bothered they have been by their AD over the past 24 hours at the time of completion. A 5-point categorical response scale will be used ('not at all', 'slightly', 'somewhat', 'a lot', 'very much'). Subjects will complete this item as part of the eDiary each day in the morning from Week -2 (visit 2) until Week 52. The PGI-B is included in the investigator trial file.

10.3.2.5 Patient Global Impression of Severity

The Patient Global Impression of Severity (PGI-S) is a single item designed to capture the subject's perception of overall eczema symptom severity over the last 24 hours on a 4-point categorical response scale ('no symptoms' to 'severe'). Subjects will complete this item as

part of the eDiary each day in the morning from Week -2 (visit 2) until Week 52. The PGI-S is included in the investigator trial file.

10.3.2.6 Patient-Oriented Eczema Measure

The Patient-Oriented Eczema Measure (POEM) is a validated questionnaire used to assess disease symptoms in atopic eczema patients in both clinical practice and clinical trials (21). 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 according to the SoP in Section 4. It will be completed electronically on the device supplied to the trial site and is included in the investigator trial file.

10.3.2.7 Dermatology Life Quality Index

The Dermatology Life Quality Index (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 HQoL over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment (22). 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 HQoL. The DLQI will be completed according to the SoP in Section 4. It will be completed electronically on the device supplied to the trial site and is included in the investigator trial file.

10.3.2.8 EQ-5D-5L

The EuroQoL 5-Dimension Health Questionnaire 5 Level (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 (23). 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 according to the SoP in Section 4. It will be completed electronically on the device supplied to the trial site and is included in the investigator trial file.

10.3.2.9 SF-36

The SF-36v2 (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 (32).

The SF-36v2 (Acute Recall) 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 according to the SoP in Section 4. It will be completed electronically on the device supplied to the trial site and is included in the investigator trial file.

10.3.2.10 Work Productivity and Activity Impairment – General Health

The impact of AD on the subject's ability to work and perform regular activities will be assessed by Work Productivity and Activity Impairment – General Health (WPAI-GH). The WPAI-GH questionnaire is an instrument to measure impairments in both paid work and unpaid work (40). It consists of 6 items and measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problem during the past 7 days. The following 4 main outcomes can be generated from the WPAI-GH:

- Percent work time missed due to health for those who were currently employed.
- Percent impairment while working due to health for those who were currently employed and actually worked in the past 7 days.
- Percent overall work impairment due to health for those who were currently employed.
- Percent activity impairment due to health for all respondents.

The WPAI-GH will be completed electronically on the device supplied to the trial site according to the SoP (Section 4) and is included in the investigator trial file.

10.3.2.11 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a Likert-scale tool widely used to detect states of anxiety and depression in a general hospital setting (24). 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 SoP (Section 4) and is included in the investigator trial file.

10.3.2.12 Treatment Satisfaction Questionnaire for Medicine

The Treatment Satisfaction Questionnaire for Medicine (TSQM) v. II is a generic questionnaire assessing subjects' satisfaction with the treatment (30). The tool consists of 11 items addressing effectiveness, side effects, convenience and overall satisfaction. The TSQM will be completed electronically on the device supplied to the trial site according to the SoP (Section 4) and is included in the investigator trial file.

10.4 Safety assessments

10.4.1 Vital signs

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

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

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 as false. If the third measurement confirms the first measurement (abnormal) the second measurement will be considered as false. Only the last value measured and considered as correct will be recorded in the eCRF.

Clinically significant abnormal vital signs at the (first) screening visit will be documented as medical history in the eCRF (refer to Appendix 4D for further details). If an abnormal vital sign at any other visit than the first screening visit is considered by the investigator to be clinically significant, it will be reported as an AE in accordance with the principles for data entry (Appendix 4D).

10.4.2 Physical examination

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

Refer to Appendix 4D for principles for data entry into the eCRF.

10.4.3 Digital ECG

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

A pre-evaluation of the ECGs will be performed by the investigators to evaluate immediate subject safety. At a minimum, 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 investigator has the final decision on the clinical significance of ECG abnormalities. If a result is abnormal at the screening visit and considered by the investigator to be clinically significant, it will be up to 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. Refer to Appendix 4D for principles for data entry in the eCRF.

Test dummy transmissions will be undertaken prior to trial conduct to ensure that transmissions can be made and that date and time settings are correctly set.

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

10.4.4 Pregnancy test

A serum pregnancy test must be taken at the screening visit in female subjects of child-bearing potential as described in the SoP in Section 4.

A urine pregnancy test (human chorionic gonadotropin; dipstick) must be performed at the trial site at baseline prior to randomisation in female subjects of child-bearing potential. The test must be repeated every 4 weeks as shown in the SoP in Section 4.

Note that pregnant subjects must discontinue IMP immediately (Section 9.8.1).

10.4.5 Laboratory testing

The following safety samples will be analysed by a central laboratory: chemistry, haematology, serology, and serum pregnancy (Panel 13). 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.

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

Samples for laboratory testing will be collected according to the SoP (Section 4).

Panel 13 Central laboratory testing

Chemistry	Haematology
Sodium Potassium Creatinine Urea nitrogen Calcium Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Gamma glutamyl transferase Bilirubin[1] Lactate dehydrogenase Cholesterol LDL cholesterol HDL cholesterol Triglycerides Glucose (non-fasting) Albumin Protein Tryptase[2]	Erythrocytes Hematocrit Hemoglobin Erythrocyte mean corpuscular volume Erythrocyte mean corpuscular haemoglobin concentration Leukocytes Neutrophils, neutrophils/total cells Lymphocytes, lymphocytes/total cells Monocytes, monocytes/total cells Eosinophils, eosinophils/total cells Basophils, basophils/total cells Thrombocytes
	Serology
	Hepatitis B virus surface antigen[4] Hepatitis B virus surface antibody[4] Hepatitis B virus core antibody[4] Hepatitis C virus antibody[4] HIV-1 antibody[4] HIV-2 antibody[4] Immunoglobulin E[5]
Urinalysis[3]	**Serum pregnancy test (females only)[4]**
Protein Glucose Ketones Occult blood Leukocytes Nitrite	Choriogonadotropin beta

1) If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
2) Only measured in case of suspected anaphylaxis (Section 9.2).
3) Urine samples will be tested at the trial site (dipstick). In case of abnormal dipstick results, a urine sample will be sent to the central laboratory for microscopic examination (leukocytes, erythrocytes, and casts).
4) Measured at screening only.
5) Not measured at screening.

HDL, high density lipoprotein; LDL, low density lipoprotein.

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

The central laboratory will provide results in conventional units to trial sites in the US and in SI units to trial sites in Europe and Asia; results that are transferred to the trial database will be in conventional and SI units.

Handling, storage, destruction and shipment instructions are provided in a separate laboratory manual.

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 enrolled into the trial (respecting exclusion criteria no. 26, 27, and 28).

10.4.6 Pharmacokinetic assessments

Blood samples for PK assessments must be collected at the time points specified in the SoP (Section 4). Note that at Week 15, a blood sample for PK will be drawn but no assessments that require trial personnel will be performed.

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.

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).

10.4.7 Anti-drug antibodies measurements

Blood samples will be collected for determination of anti-tralokinumab antibody levels at pre-determined time points according to the SoP (Section 4).

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

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

10.5 Other assessments and photography

10.5.1 Skin microbiology

10.5.1.1 Background and rationale

Normal skin is colonised by a wide variety of microorganisms, including fungi, viruses, and bacteria. The skin microbiome is complex and diverse, and varies between individuals and anatomical sites (37). It has been known for years that some skin diseases are associated with dysbiosis of the skin microbiome. AD, in particular, has long been associated with increased skin colonisation with S. aureus. Indeed, S. aureus colonisation has been proposed to play an important role in AD pathophysiology via bacterial production of specific virulence factors (38). Increased colonisation with S. aureus in AD is accompanied by decreased colonisation with many commensal bacterial species, resulting in overall decreases in bacterial diversity (39). Resolution of active disease in AD in response to therapy correlates with reduction of S. aureus colonisation and increases in microbiome diversity (39).

A recent phase 2b trial in subjects with moderate-to-severe AD who were sampled with skin swabs on lesional skin showed a reduced frequency of S. aureus positive subjects following treatment with tralokinumab compared with placebo. A similar evaluation will be performed in the present trial. Since global analyses of microbiome diversity were not undertaken in the phase 2b tralokinumab trial, the present trial will use gene sequencing to identify specific strains of bacteria present on the skin and thus characterise treatment effects on the skin microbiome in AD subjects.

10.5.1.2 Staphylococcus aureus colonisation (all subjects)

Samples (skin swabs) from a representative lesion will be taken from all subjects to detect presence or absence of S. aureus colonisation. Samples will be collected according to the SoP (Section 4) and the body location will be documented in the eCRF (upper limb, lower limb, trunk, head). Efforts will be made to swab the same skin site (lesion) at all time-points, even if the lesion has cleared.

S. aureus colonisation will be determined using an RNA-based method (quantitative real-time polymerase chain reaction). This will provide data on treatment effects on subclinical infections with S. aureus that is very frequent in AD patients.

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

10.5.1.3 Skin microbiome characterisation (selected trial sites)

At selected trial sites, subjects will be asked to participate in an exploratory component involving skin microbiome characterisation. Participation in this exploratory component which also includes skin biopsies and additional serum biomarker testing requires that the subject provides additional informed consent.

Skin swabs will be taken from a representative lesion. Samples will be collected according to the SoP (Section 4) and the same lesion will be sampled throughout the trial. The location of the lesion will be documented in the eCRF (upper limb, lower limb, trunk). Isolates will be cultured and the microbiome will be characterised using next-generation sequencing.

Subjects should not shower, bathe, or otherwise wash the lesion where the swab will be taken from within 12 hours of sample collection.

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

Since subjects will also have skin biopsies taken from the lesion selected for microbiome characterisation, the trial will provide a unique opportunity to combine gene expression, histology, and microbiome data from the same lesions in AD subjects. The results will help to clarify the role of IL-13 pathways in regulation of the skin microbiome and may shed light on the role of the microbiome in the pathophysiology of AD.

The skin microbiome results will not be included in the CTR but will be presented in a separate report.

10.5.2 Serum biomarkers

10.5.2.1 Rationale

Serum biomarkers will be evaluated as an exploratory part of the tralokinumab phase 3 programme to profile the molecular response and to identify subpopulations of AD patients with increased response to treatment.

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

The biomarker results from the small panel will be presented in the CTR, whereas results from the large panel (assessed at selected trial sites) will be presented in a separate report.

10.5.2.2 Small biomarker panel (all subjects)

All subjects will have blood samples taken for analysis of a small panel of biomarkers. The biomarkers to be analysed include, but are not limited to, the following: periostin, DPP4, CCL17 (also known as thymus and activation regulated chemokine [TARC]), IL-13, IL-17, IL-22, and beta-defensin 4A (DEFB4A). These samples will be taken according to the SoP (Section 4). LEO may only analyse samples from a subset of subjects.

10.5.2.3 Large biomarker panel (selected trial sites)

At selected trial sites, subjects will be asked to participate in additional biomarker testing. Participation in this component of the trial which also includes skin microbiome characterisation and skin biopsies requires that the subject provides additional informed consent.

Subjects consenting to additional biomarker testing will have an extra blood sample taken to measure additional serum biomarkers. These samples will be taken according to the SoP (Section 4). To allow unbiased biomarker discovery, a large panel of biomarkers will be assessed.

10.5.3 Skin biopsies (selected trial sites)

At selected trial sites, subjects will be asked to participate in an exploratory component involving skin biopsies. Participation in this component of the trial which also includes skin microbiome characterisation and additional serum biomarker testing requires that the subject provides additional informed consent.

Two 3 mm skin biopsies (1 for histology, 1 for gene expression analysis) must be taken from lesional skin at the time-points specified in the SoP (Section 4). At baseline, 2 skin biopsies will also be taken from non-lesional skin at an anatomically similar site (i.e., a total of 4 biopsies at baseline). The lesional skin biopsies must be taken from the same lesion used for microbiome characterisation (Section 10.5.1.3). The body location of each site will be documented in the eCRF (upper limb, lower limb, trunk).

A check of skin biopsy wound healing including removal of suture, if applicable, will be performed at the next trial visit (i.e., at Weeks 2, 6, and 18).

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

The biopsies will be analysed for expression of markers of inflammation and skin barrier integrity by histology/immunohistochemistry and gene expression analysis.

The biomarkers to be analysed include, but are not limited to, the following:

Histology/immunohistochemistry/in-situ hybridisation

- T cells (e.g., CD3+ and CD8+), dendritic cells (e.g., CD11c+, FcεR1), monocytes/macrophages (e.g., CD68), epidermal markers (e.g., epidermal thickness, keratin type I cytoskeletal 16, proliferation marker protein Ki-67, protein S100-A, filaggrin, loricrin).

Gene expression analysis

- Global gene expression analysis by RNA sequencing.
- Quantitative real-time polymerase chain reaction (qPCR) analysis of the following genes: IL-1B, IFNG, IL-13, IL-31, CCL17 (TARC), CCL26, C-X-C motif chemokine ligand 10 (CXCL10), IL-12/IL-23p19, IL-17A, CCL20, IL-19, IL-20, IL-22, S100A9, S100A12.

Rationale for selection of biomarkers in biopsies
The biomarkers to be analysed in the biopsies have been selected to assess the effect of IL-13 inhibition on cell types and cytokines that play a key role in AD skin. Effective treatments of AD are known to reduce the number of inflammatory cells in lesional skin as well as to modulate epidermal markers towards a non-diseased phenotype (25). A quantitative real-time polymerase chain reaction analysis of markers of specific subsets of T cells (e.g., Th1, Th2, Th17, and Th22) will allow analysis of the mechanism of action of tralokinumab in diseased AD skin.

Overall, the results from the analyses of biopsy material will be included in the CTR, except the global gene expression analysis which will be presented in a separate report.

10.5.4 Storage of biological samples

Samples collected as part of the exploratory component (microbiome characterisation, biomarkers, and skin biopsies) will be retained for as long as the quality of the material permits evaluation but for no longer than 12 months after completion of the CTR unless specific additional consent has been obtained that allows storage for future research (see below).

Biobank
This protocol includes the collection and analysis of different biological samples. If consent is given by the subject, LEO will store samples collected as part of the exploratory component

(i.e., serum samples for biomarker analysis and skin biopsies) in the biobank established by LEO and hosted by BioStorage Technologies, Inc. The residual biological samples will be used for future research performed by LEO. Donation of the samples for future research is voluntary and subjects must give their separate written consent to confirm donation and storage and the terms associated herewith. The samples will be transferred from the relevant laboratory to the biobank. The samples will be labelled with the trial ID, subject ID, and the sample date to protect the privacy of the subjects and to allow continued blinding for future analyses. The samples from this trial will be stored for 10 years after the end of the trial and will then be destroyed.

10.5.5 Photography (selected trial sites)

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 a representative lesion according to the SoP (Section 4).

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

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

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

LEO 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.

10.6 Estimate of total blood volume collected

Blood samples will be drawn for safety (chemistry, haematology, serology, PK, ADA) and biomarkers. The total volume of blood to be withdrawn is approximately 435 mL which is less than the volume of blood drawn during a blood donation (approximately 500 mL).

11 Adverse events

AEs and serious adverse events (SAEs) are defined in Appendix 2.

Classification of AEs in terms of severity, causality and outcome are defined in Appendix 3.

11.1 Collection of adverse events

AEs must be collected from time of first trial-related activity after the subject has signed the informed consent form until completion of the clinical trial (defined as the safety follow-up visit 16 weeks after last injection). For subjects entering the long-term extension trial (LP0162-1337, ECZTEND), any (S)AE with onset before the final visit in the LP0162-1325 trial should be reported LP0162-1325. 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 Appendix 4D for principles for data entry in the eCRF.

11.2 Reporting of adverse events

AEs reported by the subject or observed by the investigator must be recorded on the AE form of the CRF 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. 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 3.

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

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

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

11.3 Reporting of serious adverse events

The criteria that define an AE as serious (i.e., an SAE) are defined in Appendix 2.

11.3.1 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 IMP, comparator or 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 Pharmacovigilance, LEO using the e-mail address or fax number below:

Global Pharmacovigilance, LEO

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

Fax number: +45 7226 3287

It may be relevant for the investigator to enclose other information with the SAE form, such as anonymised reports of diagnostic procedures, hospital records, autopsy reports, etc.

Additionally, Global Pharmacovigilance, 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 institutional review board(s) (IRB[s])/ independent ethics committee(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 safety follow-up visit [FU1/FU2]) should not be routinely sought or collected. However, such events should be reported to LEO (see contact details above) if the investigator becomes aware of them.

11.3.2 LEO reporting responsibilities

Global Pharmacovigilance, LEO is responsible for assessing whether or not an SAE is expected. The relevant reference document for this clinical trial is:

For the IMP, the Investigator's Brochure, edition 16 and subsequent updates must be used.

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

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

For all countries except the US, all SAEs which are assessed as causally related to the IMP(s) 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 IRB(s)/IEC(s) according to the current applicable legislation in the concerned countries. Investigators will be notified of such SUSARs and the evolving safety profile on an ongoing basis.

For the US, as per Guidance for Industry and Investigators - Safety Reporting Requirements for INDs and BA/BE Studies, only those events for which the sponsor determines there is a reasonable possibility of a causal relationship are subject to IND Safety Reporting. Investigators will be notified of the evolving safety profile on an ongoing basis.

11.4 Other events that require expedited reporting

11.4.1 Pregnancy

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

The completed Pregnancy Follow Up Forms must be faxed or scanned and e-mailed to Global Pharmacovigilance, LEO. Contact details are given in Section 11.3.1.

Pregnant subjects must permanently discontinue IMP (see Section 9.8.1).

11.5 Reporting of other events

11.5.1 Adverse events of special interest

The events listed in Panel 14 are considered adverse events of special interest (AESIs) in this trial and will require that the investigator provides additional information to LEO. An AESI may be serious (requiring expedited reporting, Section 11.3) or non-serious.

Panel 14 Adverse events of special interest

Adverse event of special interest	**Additional information to be provided (if available[1])**
Eczema herpeticum	Skin findings: • Lesion type. • Disseminated / localised. • Location. • Present in an area with visible eczema / no visible eczema / present in areas with and without eczema. • Monomorphic / polymorphic. Confirmation of herpes simplex virus
Malignancies diagnosed after randomisation, excluding basal cell carcinoma, localised squamous cell carcinoma of the skin, and carcinoma in situ of the cervix	Histology report Oncology assessment Treatments (surgery, radiation, chemotherapy, other)
Skin infections requiring systemic treatment	Skin swab • Outcome.
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

Adverse event of special interest	**Additional information to be provided (if available[1])**
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.

11.5.2 Overdose

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

The term overdose must be documented on the AE form of the CRF. In addition, AEs originating from overdose must be documented on a separate line.

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

11.5.3 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 four categories: wrong medication, wrong dose (including strength, form, concentration, amount), wrong route of administration, or wrong subject.

The medication error 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 specifying the category of error (see definitions above).

If the medication error is due to device malfunction, such malfunction must be reported as a device complaint as described in Section 9.11.

11.5.4 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.

11.5.5 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.

11.5.6 Aggravation of condition

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

11.6 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, i.e. the follow-up may continue beyond the end of the clinical trial. For SAEs which have stabilised and cannot be expected to recover during study or safety follow-up periods, for example chronic illnesses, the final outcome should be considered recovered and a statement that the SAE has stabilised should be added to the narrative in the SAE form.

11.7 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 within the EU Directive 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.*" (33).

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 authority(ies), or IRB(s)/IEC(s).

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.

12 Statistical methods

12.1 Sample size

A total of 780 subjects will be randomised 3:1 to initial treatment in this trial (585 subjects in the tralokinumab arm; 195 subjects in the placebo arm). The sample size is chosen to ensure that sufficient safety information is collected and to ensure a sufficient number of responders are re-randomised to maintenance treatment.

The primary endpoints for initial treatment IGA 0/1 and EASI75 at Week 16 are to be evaluated hierarchically testing both hypotheses of no difference between active and placebo at the 5% significance level. The hypothesis for IGA 0/1 will be tested first; if significant, the EASI75 hypothesis will be tested.

For the endpoint IGA 0/1 at Week 16, a sample size of 780 subjects randomised at 3:1 will provide >99% power to detect a difference between the 2 arms of 30% for tralokinumab and 10% for placebo at a 5% 2-sided level of significance. For the endpoint EASI75 at Week 16 a sample size of 780 will likewise provide >99% power to detect a difference between tralokinumab and placebo at Week 16, assuming EASI75 response rates of 40% and 15%, respectively.

With an IGA response rate of 30% at Week 16, 175 IGA responders initially treated with tralokinumab are expected to enter the maintenance treatment period (70 subjects on tralokinumab Q2W, 70 subjects on tralokinumab Q4W, 35 subjects on placebo). Assuming IGA response rates at Week 52 of 80%, 50% and 5%, respectively for Q2W, Q4W, and placebo, the power to show a difference at the 4% significance level will be >99% between Q2W and placebo and >99% between Q4W and placebo.

With an EASI75 response rate of 40% at Week 16, 235 EASI75 responders initially treated with tralokinumab are expected to enter the maintenance treatment period (94 subjects on tralokinumab Q2W, 94 subjects on tralokinumab Q4W, 47 subjects on placebo). Assuming EASI75 response rates at Week 52 of 90%, 55% and 5%, respectively for Q2W, Q4W, and placebo, the power to show a difference at the 4% significance level will be >99% between Q2W and placebo and >99% between Q4W and placebo.

12.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All subjects randomised to initial treatment are included in the full analysis set and will be analysed for efficacy up to Week 16 (visit 12). Exclusions from the full analysis set can be considered in special cases as described in ICH E9, Section 5.2.1, Full Analysis Set. If it is decided to exclude a randomised subject from the full analysis set, a justification addressing ICH E9 will be given.

A per protocol analysis set will be used as an efficacy subset for the analysis of the primary endpoints up to Week 16 (visit 12), and analyses based on the per protocol analysis set will be performed to support the results obtained for the full analysis set. The per protocol analysis set will be defined by excluding subjects from the full analysis set for whom any of the following conditions apply:

- Receive no treatment with the IMP.
- Provide no assessment of IGA or EASI following start of treatment.
- Are known to have taken the wrong IMP throughout the initial treatment period of the trial.
- Do not fulfil all the inclusion criteria no. 3, 6, 7 and 8.

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

A safety analysis set will be defined by excluding subjects from the full analysis set who either received no treatment with IMP and/or for whom no post-baseline safety data are available.

A maintenance safety analysis set will be defined as subjects in the full analysis set who are re-randomised to maintenance treatment at Week 16 (visit 12) and who have safety data available after Week 16.

An open-label safety analysis set will be defined as subjects in the full analysis set who are still in the trial at Week 16 (visit 12), who have safety data available after Week 16 and who at any point in time enter the open-label treatment arm.

Based on the above-mentioned rules, the inclusion/exclusion of subjects from the trial analysis sets will be documented in the statistical analysis plan update before breaking the randomisation code.

12.3 Statistical analysis

12.3.1 Disposition of subjects

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

12.3.2 Demographics and other baseline characteristics

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

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

12.3.3 Exposure and treatment compliance

12.3.3.1 Exposure

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

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

12.3.3.2 Treatment compliance

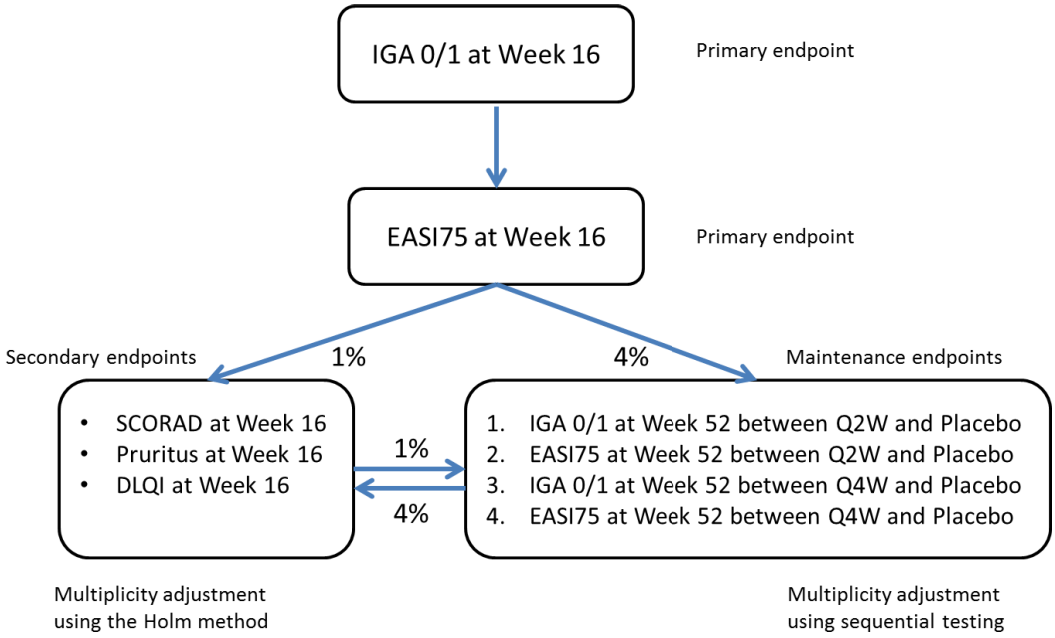
Adherence to treatment regimen will be recorded in the eCRF. Where home-use is appropriate, the subject will be asked at each trial visit if IMP was administered as instructed. The log of drug administration may be used as source. If any complications or deviations in administration are observed, these will be described as protocol deviations.

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

12.3.4 Multiple testing procedure

To control the overall type 1 error rate, the primary analyses of the primary estimands for the primary and secondary endpoints for the initial and maintenance treatment will follow the testing procedure outlined in Panel 15. The hypothesis relating to a specific endpoint cannot be rejected unless all hypotheses relating to endpoints earlier in the hierarchy are also rejected.

Panel 15 Testing procedure for primary, secondary, and maintenance endpoints



Arrows indicate order of testing when superiority is shown for all endpoints within a box.
DLQI, Dermatology Life Quality Index; EASI75, at least 75% reduction in Eczema Area and Severity Index score; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks.

The procedure will be as follows:

IGA 0/1 at Week 16 between tralokinumab and placebo is evaluated at a 5% significance level. If the test is significant, EASI75 at Week 16 between tralokinumab and placebo is evaluated at a 5% significance level.

If both these tests are significant, the significance level (alpha) will be split between the analyses of the 3 secondary endpoints at Week 16 and the analyses of the 2 maintenance endpoints at Week 52. These groups of tests are tested in parallel with alpha=1% for the endpoints at Week 16 and with alpha=4% for the maintenance endpoints at Week 52.

The evaluations of the 3 secondary endpoints at Week 16 between tralokinumab and placebo will use the Holm method (26) for 3 ordered p-values at a 1% significance level to adjust for multiplicity.

The hypotheses for the maintenance treatment endpoints will be tested sequentially in the specified order at the 4% significance level. The next hypothesis will only be tested if the former was significant.

If all p-values for the 3 secondary endpoints at Week 16 are significant, then the hypotheses for the maintenance treatment endpoints can be evaluated at a 5% significance level. Conversely, if all p-values for the maintenance endpoints are significant, then the hypotheses for the 3 secondary endpoints at Week 16 can be evaluated at a 5% significance level.

12.3.5 Analysis of initial treatment

12.3.5.1 Analysis of primary endpoints

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

- Primary estimand: ‘composite’.
- Secondary estimand: ‘hypothetical’.
- Tertiary estimand: ‘treatment policy’.

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

- **Initiation of rescue medication**: Some of the estimands use the initiation of rescue medication as an event that modifies the applied value of an endpoint, e.g. by defining a subject receiving rescue medication as a non-responder.
- **Permanent discontinuation of IMP**: This event occurs when a subject is permanently withdrawn from the treatment or the trial as described in Section 8.5. This can either happen at his/her own initiative or at the investigator's discretion. The event also includes the possibility of a subject being lost to follow-up. The timing of the event is defined as the date of the early termination visit for withdrawn subjects or – in the case of a subject lost to follow-up – the date of the last known visit to the clinic. As for the rescue medication, the event type is used to modify an applied endpoint value.

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

12.3.5.1.1 Primary estimand: 'composite'

The primary estimand for the primary endpoints will be:

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

The primary estimand assesses the expected difference in response rates (defined as response obtained without initiation of any rescue medication) after 16 weeks, resulting from initiation of a treatment regimen with tralokinumab compared to a treatment regimen with placebo.

Primary analysis for the primary estimand

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

The difference in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test stratified by region (North America, Japan, and Europe) and baseline disease severity (IGA 3 or 4). The treatment estimate and the corresponding 95% CI

will be presented. The null hypothesis of no difference in response rates between tralokinumab and placebo will be tested against the 2-sided alternative that there is a difference.

The primary endpoints will be tested sequentially at a 5% significance level. IGA 0/1 will be tested first, and, if significant, then EASI75 will be tested. If both primary null hypotheses are rejected, the secondary endpoints and the maintenance endpoints will be tested.

Sensitivity analyses for the primary estimand

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

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

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

Sensitivity analysis 2: Rather than imputing all subjects who do not attend the Week 16 visit and where rescue medication has not been used as non-responders, the following approach will be applied. If subjects have withdrawn due to an AE or due to lack of efficacy, they are still considered non-responders. Data missing for other reasons will be imputed using last observation carried forward (LOCF), hereby assuming that the last value is a more reliable estimate of the missing response (than a non-response).

Supplementary analysis

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

12.3.5.1.2 Secondary estimand: ‘hypothetical’

The secondary estimand for the primary endpoints will be:

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

The secondary estimand assesses the expected difference in response rates achieved when adhering to the treatment regimen tralokinumab with no rescue medication as compared to a treatment regimen with placebo with no rescue medication.

Primary analysis of the secondary estimand

Data collected after permanent discontinuation of IMP or after initiation of rescue medication will not be applied in the analysis.

IGA 0/1 responder imputation

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

1. In each group, intermittent missing values will be imputed using LOCF to obtain a monotone missing data pattern.
2. An ordinal logistic regression model assuming proportional odds will be fitted to the IGA value at Week 2. The model will include effects of region, 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=11109925).
3. For each of the 100 copies of the dataset, missing values at Week 4 will be imputed in the same way as for Week 2. The imputations will be based on a proportional odds logistic regression model with effects of region and baseline disease severity (IGA 3 or 4) together with the IGA value at Week 2 as factors. The estimated parameters, and their variances, will be used to impute missing values at Week 4.
4. This stepwise procedure will then be repeated sequentially for Week 6, 8, 10, 12, 14, and 16 with the modification that only the IGA values from the two preceding visits will be included as factors in addition to region and baseline disease severity. The missing binary IGA 0/1 response at Week 16 will be derived from the corresponding underlying imputed IGA value.

EASI75 responder imputation

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

1. Intermittent missing values will be imputed in each group using a Markov Chain Monte Carlo method to obtain a monotone missing data pattern and 100 copies of the dataset will be generated (seed=29099725).
2. 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 region, and baseline disease severity (IGA 3 or 4) as factors. The estimated parameters, and their variances, will be used to impute missing EASI values at Week 2. 100 copies of the dataset will be generated (seed=11109925).
3. For each of the 100 copies of the dataset, missing EASI values at Week 4 will be imputed in the same way as for Week 2. The imputations will be based on the same ANCOVA model with effects of baseline EASI as a covariate, and region, and baseline disease severity (IGA 3 or 4) as factors together with the EASI value at Week 2 as covariate. The estimated parameters, and their variances, will be used to impute missing values at Week 4.
4. This stepwise procedure will then be repeated sequentially for Week 6, 8, 10, 12, 14, and 16 with the modification that only the EASI values from the preceding two visits will be included as covariates in addition to baseline EASI as a covariate, and region and baseline disease severity as factors. The missing binary EASI75 response at Week 16 will be derived from the corresponding underlying imputed EASI value.

Analysis of Week 16 response

For each of the 100 complete data sets, the difference in response rates (either the IGA 0/1 or the EASI75) between treatment groups will be analysed using the Cochran-Mantel-Haenszel test stratified by region (North America, Japan, and Europe) 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 secondary estimand

Rather than assuming that observations are missing at random within each treatment arm, it is assumed that missing data from subjects who discontinue IMP permanently/receive rescue

medication in the tralokinumab arm will resemble missing data from subjects from the placebo arm who do not discontinue IMP permanently/receive rescue medication. The underlying assumption is that the effect of tralokinumab following rescue medication or permanent treatment discontinuation 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 arms.

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

12.3.5.1.3 Tertiary estimand: 'treatment policy'

The tertiary estimand for the primary endpoints will be:

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

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

Primary analysis for the tertiary estimand

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

Imputation of missing data at Week 16 will be done using multiple imputations within 4 groups defined according to randomised treatment arm and whether or not subjects have permanently discontinued IMP prior to Week 16. Within a given treatment arm, retrieved data from discontinued subjects will be used to impute missing data for other discontinued subjects. Similarly, the available data from not discontinued subjects will be used to impute data for such patients where the Week 16 value is missing.

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

For discontinued subjects, it is expected that the number of subjects with retrieved data at Week 16 will be too small to facilitate the same imputation model as mentioned above.

Consequently, an imputation model with only region and baseline effects (IGA as a factor and EASI as a covariate [only for EASI75]) will be applied for discontinued subjects. Some factors may have to be omitted, depending on the observed data, e.g. if retrieved subjects only come from one region or if they all have the same baseline severity.

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

Sensitivity analyses for the tertiary estimand

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

12.3.5.2 Analysis of secondary endpoints

The 3 secondary endpoints evaluate the impact of 16 weeks of treatment on (i) severity and extent of AD, (ii) itch, and (iii) HRQoL. The corresponding endpoints are (i) the change from baseline to Week 16 in SCORAD, (ii) reduction (Y/N) 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, and (iii) change from baseline to Week 16 in DLQI score. Subject-reported worst daily itch over the last week prior to baseline will be used to calculate the baseline itch (see also inclusion criterion no. 9).

Reduction of Worst Daily Pruritus NRS weekly average of at least 4 is a binary endpoint, and it will be analysed as described for the primary endpoint EASI75 using all three 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.

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

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

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

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

Primary analysis of the primary estimand (continuous secondary endpoints)

Data collected after permanent discontinuation of IMP or after initiation of rescue medication will not be included in the analysis.

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

Change from baseline in SCORAD

= treatment × visit + baseline SCORAD × visit + region + baseline IGA

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

Sensitivity analysis for the primary estimand (continuous secondary endpoints)

Rather than assuming that observations are missing at random within each treatment arm it is assumed that missing data from subjects who discontinue treatment/receive rescue medication in the tralokinumab arm will resemble data from subjects from the placebo arm who do not discontinue treatment/receive rescue medication. Imputation of missing data at Week 16 will be done using a pattern mixture model where missing data in the tralokinumab arm as well as the placebo arm will be imputed from the placebo arm (using a so-called copy-reference approach). The procedure for the change from baseline in SCORAD at Week 16 is described below. The same procedure will be applied for the 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=29099725).

2. For each of the 100 copies of the dataset, an ANCOVA model will be fitted to the SCORAD value at Week 2 in the placebo group. The model will include effects of baseline SCORAD as a covariate, and region and baseline disease severity (IGA 3 or 4) as factors. The estimated parameters, and their variances, will be used to impute missing values at Week 2 for the placebo group as well as the tralokinumab group (seed=11109925).
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 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 Week 6, 8, 10, 12, 14, and 16 with the SCORAD values from the preceding two visits included as covariates in addition to baseline SCORAD as a covariate, and region and baseline disease severity as factors.

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

12.3.5.2.2 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 in SCORAD and DLQI, respectively, between tralokinumab and placebo regardless of rescue medication use and treatment discontinuation.

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

Primary analyses for the secondary estimand (continuous secondary endpoints)

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

Imputation of missing data at Week 16 will be done using multiple imputations within 4 groups defined according to randomised treatment arm and whether or not subjects have discontinued treatment prior to Week 16. Within a given treatment arm, retrieved data from discontinued subjects will be used to impute missing data for other discontinued subjects. Similarly, the available data from not discontinued subjects will be used to impute data for such subjects where the Week 16 value is missing.

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

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

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

Sensitivity analyses for the secondary estimand (continuous secondary endpoints)

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

Imputation of missing data at Week 16 will be done using a pattern mixture model where missing data in the tralokinumab arm as well as the placebo arm will be imputed from the placebo arm (copy-reference approach). With this exemption, the multiple imputation

procedure and analysis will be conducted in the same way as described for the primary analysis of the secondary estimand for the continuous secondary endpoints.

12.3.5.3 Analysis of additional secondary endpoints

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

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

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

To support the secondary endpoint on HQoL, the binary endpoint reduction from baseline to Week 16 of DLQI of ≥4 points will be analysed and presented for the subjects in the full analysis set with a baseline DLQI ≥4 similarly to the analysis described for the primary analysis of the primary estimand for the primary endpoints.

12.3.5.4 Analysis of other endpoints

12.3.5.4.1 Efficacy over time

To further pursue the objectives supported by the five Week 16 endpoints in the confirmatory test hierarchy, these endpoints (as well as the change in Worst Daily Pruritus NRS [weekly average]) will be evaluated at each scheduled assessment up to Week 14 or each week up to Week 15:

- IGA 0/1 at each scheduled assessment until Week 14.
- EASI75 at each scheduled assessment until Week 14.
- Change in SCORAD from baseline to each scheduled assessment until Week 14.
- Change from baseline to each week through Week 1 to 15 in Worst Daily Pruritus NRS (weekly average).
- Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to each week through Week 1 to 15.
- Change in DLQI score from baseline to each scheduled assessment until Week 14.

Nominal p-values for test of a treatment difference and 95% CI for the difference will be presented at each scheduled visit (or each week for Worst Daily Pruritus NRS) using the same approach as applied for the primary analysis of the relevant endpoint in the primary estimand.

For the binary endpoints, the same Cochran-Mantel-Haenszel test as for the Week 16 assessment will be applied. For the continuous endpoints, the repeated measurements model already described previously for the Week 16 assessments facilitates that the p-values, treatment differences and 95% CIs can be derived for each visit up to Week 14 (or Week 15 for the change in Worst Daily Pruritus NRS) in the same analysis that already will be made for the corresponding Week 16 assessments.

12.3.5.4.2 Patient-reported outcomes

The PROs POEM, DLQI, EQ-5D-5L, SF-36, WPAI-GH, HADS, and TSQM will be summarised by treatment group and visit using descriptive statistics. The summaries will be made separately for the initial treatment and the maintenance treatment. Data from the initial treatment period will be presented for the full analysis set and data from the maintenance treatment period will be presented for the maintenance analysis set.

The PROs collected in the eDiaries on a daily basis (Worst Daily Pruritus NRS, Average Daily Pruritus NRS, Eczema-related Sleep NRS, PGI-B, and PGI-S) will all be summarised over time by treatment group using descriptive statistics. The summaries will be separate for the initial treatment and the maintenance treatment. Data from the initial treatment period will be presented for the full analysis set and data from the maintenance treatment period will be presented for the maintenance analysis set.

The Average Daily Pruritus NRS collected over the last week prior to baseline will be used to calculate the baseline average daily itch. A minimum of 4 Average Daily Pruritus NRS scores out of the 7 days is required to calculate the baseline average score.

To investigate a possible early onset of itch relief, a reduction in Worst Daily Pruritus NRS weekly average of at least 3 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 endpoints.

In the subgroup of subjects with either HADS anxiety subscale score ≥8 or HADS depression subscale score ≥8 at baseline, the proportion of subjects with both HADS anxiety subscale score <8 and HADS depression subscale score <8 at Week 16 will be summarised by treatment group and analysed as described for the primary analysis of the primary estimand for the primary endpoints.

In the subgroup of subjects with a baseline POEM score of at least 4, the proportion of subjects with a reduction in POEM score of at least 4 at Week 16 will be summarised by treatment group and analysed as described for the primary analysis of the primary estimand for the primary endpoints.

The change from baseline to Week 16 in Eczema-related Sleep NRS weekly average, HADS, POEM, SF-36, WPAI-GH, and the EQ-5D-5L index will be summarised by treatment group and domain, where applicable, and analysed as described above for the primary analysis of the primary estimand of the continuous secondary endpoints. For the Eczema-related Sleep NRS score, the mean over the last 7 days prior to randomisation will be used as the baseline value.

The treatment satisfaction (TSQM) at Week 16 will be summarised by treatment group and domain and compared between treatments using an analysis of variance model including treatment, region and baseline IGA as factors.

For the PGI-B, a day of ‘no or slight bother’ is defined as answering the question with ‘not at all’ or ‘slightly’. The subjects’ number of days of ‘no or slight bother’ will be tabulated per treatment group for the initial treatment period. The mean number of days will be presented with 95% CIs and compared between the 2 treatment groups using an analysis of variance model including treatment, region, and baseline IGA as factors. In this analysis, data collected after permanent discontinuation of IMP or after initiation of rescue medication will be disregarded.

12.3.5.4.3 Skin microbiology

The incidence of skin colonisation with S. aureus will be presented by visit and treatment group for the subjects in the full analysis set. The incidence at Week 16 will be compared between the tralokinumab treatment group and the placebo group among subjects who are positive at baseline using a chi-squared test.

12.3.6 Analysis of maintenance treatment

12.3.6.1 Analysis of maintenance endpoints

For the two dichotomous maintenance endpoints, IGA 0/1 and EASI75 at Week 52, an adapted version of the primary estimand for the primary endpoints will be considered:

- Treatment difference in response rates of IGA 0/1 and EASI75 after 52 weeks achieved without rescue medication and without transfer to open-label treatment

The adapted estimand takes into account that throughout the maintenance period subjects will be actively discontinued from the treatment randomised at Week 16 and transferred to the open-label tralokinumab arm if they meet the prespecified treatment failure criteria described in Section 7.1.

This estimand assesses the expected difference in response rates (defined as response obtained without initiation of any rescue medication and without transfer to open-label treatment) after 52 weeks in patients responding to tralokinumab at Week 16 (as measured by a positive IGA 0/1 or EASI75 response), resulting from a maintenance treatment regimen with tralokinumab Q2W or tralokinumab Q4W compared to a treatment regimen with placebo.

Primary analysis for the maintenance estimand

All subjects who prior to the Week 52 visit have received rescue medication, including TCS, and/or been transferred to the open-label tralokinumab arm will be considered non-responders.

This reflects an assumption that initiation of rescue medication or transfer to open-label treatment indicates failure of the re-randomised treatment assigned at Week 16, and that a (possible) observed positive response thereafter is not attributable to the treatment received from Week 16. In addition, all subjects with missing endpoint data at Week 52 visit will be imputed as non-responders.

The 4 hypotheses of primary interest for maintenance treatment will be tested sequentially with the next hypothesis in the sequence only being tested if the previous one was significant. The multiple testing procedure planned to control the overall type 1 error rate for the trial is described in detail in Section 12.3.4. The maintenance endpoints will be evaluated in the following order:

- No difference between Q2W and placebo for IGA 0/1 at Week 52.
- No difference between Q2W and placebo for EASI75 at Week 52.
- No difference between Q4W and placebo for IGA 0/1 at Week 52.
- No difference between Q4W and placebo for EASI75 at Week 52.

For the IGA 0/1 endpoint, the analysis will be based on the subjects in the maintenance analysis set who obtained an IGA of 0/1 at Week 16 without rescue medication. For the EASI75 endpoint, the analysis will be based on the subjects in the maintenance analysis set who obtained an EASI75 at Week 16 without rescue medication.

For each endpoint (IGA 0/1 and EASI75 at Week 52) the estimated response rates and corresponding 95% CIs, and the pairwise treatment differences will be presented. The difference in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test stratified by region. The null hypotheses of no difference in response rates will be tested against the two-sided alternative that there is a difference.

Sensitivity analysis for the maintenance estimand

In a sensitivity analysis, data missing at Week 52 for subjects who did not receive rescue medication, did not transfer to open-label and did not withdraw from the trial due to AE or lack of efficacy will be imputed using LOCF.

Pooled analyses across both LP0162-1325 and LP0162-1326

In order to achieve more precise estimates of clinical response within treatment groups in the maintenance period, analyses of IGA 0/1 and EASI75 at Week 52 will be performed on pooled data from the 2 trials LP0162-1325 and LP0162-1326. For each endpoint (IGA 0/1 and EASI75 at Week 52) the estimated response rates and corresponding 95% CIs and the pairwise treatment differences will be presented. The difference in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test stratified by region within trial. The pooled analyses will only be presented in marketing authorisation applications.

12.3.6.2 Analysis of other maintenance endpoints

12.3.6.2.1 Time to relapse

The following 2 types of relapse will be considered and analysed:

- Relapse according to IGA: first assessment of an IGA≥2 or initiation of rescue medication after initiation of maintenance treatment among subjects in the maintenance analysis set who obtained an IGA 0/1 at Week 16 without rescue medication.

- Relapse according to EASI75: first time of not achieving EASI75 or initiation of rescue medication after initiation of maintenance treatment among subjects in the maintenance analysis set who obtained EASI75 at Week 16 without rescue medication.

Kaplan-Meier curves of time to relapse will be estimated and presented by treatment for the maintenance analysis set. In a supplementary exploratory analysis, tralokinumab Q2W vs. placebo and tralokinumab Q4W vs. placebo will be compared using a log-rank test stratified by region.

Subjects leaving the trial without meeting the relapse criteria will be censored at the date of the last assessment visit.

12.3.6.2.2 Continued treatment for non IGA responders

The number of responders according to IGA 0/1 at Week 52 will be tabulated for the subgroup of subjects in the maintenance analysis set who are re-randomised meeting the EASI75 criterion but not the IGA 0/1 criterion at Week 16.

12.3.6.2.3 Supportive maintenance

To support the maintenance objective, the response IGA 0/1 or EASI75 at Week 52 will be presented and analysed as described above for the primary analysis of the maintenance estimand for subjects in the maintenance analysis set who did not receive rescue medication prior to Week 16.

12.3.7 Analysis of safety

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

12.3.7.1 Adverse events

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

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

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

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

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

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

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

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

12.3.7.2 Vital signs

The change in vital signs (blood pressure, heart rate, body temperature) from baseline to each visit will be summarised by visit and treatment group as mean, standard deviation, median,

minimum and maximum values for the safety analysis set, the maintenance safety analysis set, and the open-label safety analysis set.

12.3.7.3 Clinical laboratory evaluation

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

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

12.3.7.4 Pharmacokinetics

All the PK samples in the trial are trough samples apart from the Week 15 sample. Area under the curve (AUC) will be calculated for subjects where all the 3 samples planned at Week 14, 15 and 16 have measurable concentrations. The C_{trough} concentration and the calculated AUC will be listed by treatment group and descriptive statistics will be provided.

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

The PK data will be merged with those from other clinical trials with tralokinumab for a population-based meta-analysis. Results of the meta-analysis will be presented in a separate pharmacometrics report outside of the CTR.

12.3.7.5 Anti-drug antibodies

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

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

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

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

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.

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

12.3.8 Interim analysis

No interim analysis is planned.

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

To support submission for regulatory approval, the trial will be unblinded once all randomised subjects have completed the Week 52 visit. All pre-specified analyses related to the initial and maintenance treatment period will be based on the data cut-off date of the last subject's Week 52 visit. The CTR will include all data from all randomised subjects from the initial and maintenance treatment period and all available data from the open-label treatment period and safety follow-up period as per data cut-off date.

Once all subjects have completed the open-label treatment period and safety follow-up period, an addendum to the original CTR will be written, summarising the final results from the open-label treatment period and safety follow-up period.

12.3.10 General principles

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

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

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

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

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

12.3.11 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: Protocol summary

Name of investigational medicinal product	Tralokinumab
Name of active substance	Human recombinant IL-13 monoclonal antibody.
Title of trial/ trial ID/ EudraCT no./ ClinicalTrials.gov no.	A randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab monotherapy in subjects with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic therapy – ECZTRA 1 (ECZema TRAlokinumab trial no. 1) / LP0162-1325 / 2016-004200-65 / NCT03131648
International coordinating investigator	Andreas Wollenberg, Prof. Dr. med. Dr. h.c.
Sponsor's name/ address	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark
Estimated number of trial sites and distribution	Approximately 130 sites in Europe, North America, and Japan.
Main objectives	Primary objective: To evaluate the efficacy of tralokinumab compared with placebo in treating moderate-to-severe AD. Secondary objectives: To evaluate the efficacy of tralokinumab on severity and extent of AD, itch, and health related quality of life compared with placebo. Maintenance objective: To evaluate maintenance of effect with continued tralokinumab dosing up to 52 weeks compared to placebo for subjects achieving clinical response at Week 16.
Methodology	Overview The trial will consist of a screening period of 2 to 6 weeks (Weeks -6/-2 to 0), an initial treatment period of 16 weeks (Weeks 0 to 16) and a maintenance treatment period of 36 weeks (Weeks 16 to 52). A 14-week off-treatment follow-up period for the assessment of safety is also included (Weeks 52 to 66). All subjects will use an emollient at least twice daily for at least 14 days before randomisation and will continue this treatment throughout the trial.

Methodology (continued)	Trial design Subjects found eligible following the screening period will be randomised 3:1 to tralokinumab 300 mg Q2W or placebo. Randomisation will be stratified by region and disease severity. Subjects achieving a clinical response at Week 16 (defined as Investigator's Global Assessment [IGA] of 0 or 1 on a 5-point scale ranging from 0 [clear] to 4 [severe], or at least 75% reduction in Eczema Area and Severity Index [EASI] score from baseline [EASI75]) will continue into maintenance treatment that will continue until Week 52. Subjects randomised to tralokinumab in the initial treatment period will be re-randomised 2:2:1 to one of the following Q2W maintenance regimens stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1): • Tralokinumab 300 mg Q2W. • Alternating dose administrations tralokinumab 300 mg and placebo ('tralokinumab Q4W'). • Placebo. Subjects randomised to placebo in the initial treatment period who achieve a clinical response at Week 16 (defined by IGA of 0 or 1, or EASI75) will continue to receive placebo Q2W in the maintenance treatment period. Subjects not achieving a clinical response at Week 16 as well as those who meet the criteria listed below during maintenance treatment will be transferred to open-label tralokinumab 300 mg Q2W treatment with optional use of TCS up to Week 52. *Transfer to open-label treatment* Subjects with IGA=0 at Week 16: IGA of at least 2 and not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits). Subjects with IGA=1 at Week 16: IGA of at least 3 and not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits). Subjects with IGA >1 at Week 16: not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits). *For selected countries* Subjects transferring to open-label treatment will have the option to self-administer tralokinumab in their home after adequate training (at 3 dosing visits in the open-label period after additional consent has been obtained) by site staff at the investigator's discretion. *For selected countries* Subjects who join the open-label tralokinumab arm at Week 16 will continue an additional 16 weeks of open-label treatment in order to secure at least 52 weeks of active therapy (Week 52 to Week 68).
Number of subjects to be enrolled	A total of 780 subjects will be randomised 3:1 to initial treatment (585 subjects to tralokinumab; 195 subjects to placebo).

Main criteria for inclusion	• Age 18 and above. • Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD. • Diagnosis of AD for ≥1 year. • Subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable. • AD involvement of ≥10% body surface area at screening and baseline. • An EASI score of ≥12 at screening and 16 at baseline. • An IGA score of ≥3 at screening and at baseline. • A Worst Daily Pruritus numeric rating scale (NRS) average score of ≥4 during the week prior to baseline. • Stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.
Main criteria for exclusion	• Active dermatologic conditions that may confound the diagnosis of AD. • Use of tanning beds or phototherapy within 6 weeks prior to randomisation. • Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomisation. • Treatment with TCS and/or TCI within 2 weeks prior to randomisation. • Active skin infection within 1 week prior to randomisation. • Clinically significant infection within 4 weeks prior to randomisation. • A helminth parasitic infection within 6 months prior to the date informed consent is obtained. • Tuberculosis requiring treatment within the 12 months prior to screening. • Known primary immunodeficiency disorder.
Investigational medicinal products	<u>Tralokinumab</u> 150 mg/mL solution for subcutaneous (SC) injection in an accessorised pre-filled syringe, 1.0 mL fill volume. Each kit contains 1 syringe. <u>Placebo</u> Placebo solution for SC injection in an accessorised pre-filled syringe, 1.0 mL fill volume. Each kit contains 1 syringe.
Duration of treatment	Screening period (including wash-out, if applicable) up to 6 weeks, treatment period of 52 weeks (or 68 weeks in selected countries), follow-up period of 14 weeks (subjects may enter the long-term extension trial [LP0162-1337, ECZTEND], at any time during the safety follow-up period).

Main assessments	<u>Investigator assessments</u> • Investigator's Global Assessment (IGA). • Eczema Area and Severity Index (EASI). • Scoring Atopic Dermatitis (SCORAD). <u>Subject assessments</u> A total of 12 patient-reported outcomes (PROs) will be collected. The following 5 PROs will be assessed on a daily basis using an electronic diary: Worst Daily Pruritus NRS, Average Daily Pruritus NRS, Eczema-related Sleep NRS, Patient Global Impression of Bother (PGI-B), and Patient Global Impression of Severity (PGI-S). The following 7 PROs will be completed at the trial site during visits: Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), EQ 5D 5L, SF 36 (acute recall), Work Productivity and Activity Impairment – General Health (WPAI GH), Hospital Anxiety and Depression Scale (HADS), and Treatment Satisfaction Questionnaire for Medicine (TSQM). <u>Safety assessments</u> Vital signs, physical examination, ECG, laboratory testing, pharmacokinetics (PK), anti-drug antibodies, and adverse event reporting. <u>Other assessments</u> Assessment of skin colonisation with Staphylococcus aureus, skin microbiome characterisation, serum biomarkers, skin biopsies, photographs.
Primary endpoints	• IGA score of 0 (clear) or 1 (almost clear) at Week 16. • EASI75 at Week 16.
Secondary endpoints	<u>Secondary endpoints</u> • Change in SCORAD from baseline to Week 16. • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to Week 16. • Change in DLQI score from baseline to Week 16. <u>Additional secondary endpoints</u> • AE/SAE frequency by preferred term. • Frequency of anti-drug antibodies. • EASI50 at Week 16. • EASI90 at Week 16. • Change from baseline to Week 16 in EASI score. • SCORAD75 at Week 16. • SCORAD50 at Week 16. • Change from baseline to Week 16 in Worst Daily Pruritus NRS (weekly average). • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 3 from baseline to Week 16. • Reduction from baseline to Week 16 of DLQI of ≥4 points among subjects with baseline DLQI ≥4.

Secondary endpoints (continued)	Maintenance endpoints • IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab. • EASI75 at Week 52 among subjects with EASI75 at Week 16 achieved without rescue medication after initial randomisation to tralokinumab.
Statistical methods	Primary endpoints The difference in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test stratified by region and disease severity. The primary endpoints will be tested sequentially at a 5% significance level. First IGA 0/1 and, if significant, EASI75. If both primary null hypotheses are rejected, the secondary endpoints will be tested. Secondary endpoints The change from baseline to Week 16 in SCORAD will be analysed using a repeated measurements model on the post baseline responses up to Week 16. Reduction of Worst Daily Pruritus NRS weekly average of at least 4 is a binary endpoint, and as such it will be analysed as described for the primary endpoint. Change from baseline to Week 16 in DLQI will be analysed the same way as change in SCORAD. Maintenance endpoints The 4 hypotheses of primary interest for maintenance treatment will be tested sequentially with the next hypothesis in the sequence only being tested if the previous one was significant. The maintenance endpoints will be evaluated in the following order: • No difference between Q2W and placebo for IGA 0/1 at Week 52. • No difference between Q2W and placebo for EASI75 at Week 52. • No difference between Q4W and placebo for IGA 0/1 at Week 52. • No difference between Q4W and placebo for EASI75 at Week 52. For each endpoint (IGA 0/1 and EASI75 at Week 52) the estimated response rates and corresponding 95% CIs, and the pairwise treatment differences will be presented. The difference in response rates between treatment groups will be analysed using the Cochran Mantel-Haenszel test stratified by region. A multiple testing procedure to control the overall type 1 error rate for the trial will be used.

Appendix 2: 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, or reasons for admission to hospital or surgical procedures unless these were planned before enrolment. It also includes AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP. In addition, any laboratory abnormality assessed as clinically significant by the investigator must be recorded as an AE.

Serious adverse event definition

An SAE is any untoward medical occurrence that

- results in death.
- is life-threatening.
- requires inpatient hospitalisation or prolongation of existing hospitalisation. Planned hospitalisation or planned prolonged hospitalisation do not fulfill 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 hospitalization, development of drug dependency or drug abuse.

Appendix 3: 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 following:

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

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

Outcome

The *outcome* of the event should be classified and handled as follows:

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.

Appendix 4: Trial governance considerations

Appendix 4A: 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 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Current version of applicable ICH Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

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

The protocol, protocol amendments, subject information leaflet including the informed consent form (ICF), Investigator's Brochure, and other relevant documents (for example advertisements) must be submitted to an IRB/IEC by the investigator (in collaboration with LEO, if applicable) and reviewed and approved by the IRB/IEC prior to enrolment of subjects.

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

The investigator will be responsible for the following:

- 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 4B: Informed consent process

Subjects shall 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 must be obtained prior to any clinical trial related procedure being carried out in accordance with ICH GCP (4.8) and all applicable laws and regulations. The authorised person obtaining the informed consent must also sign the ICF.

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

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

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 IWRS cannot be performed.

Appendix 4C: 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.

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.

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

The subject must be informed that his/her 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 age, gender, health condition, height, medical history, test results, etc.) which shall be collected as part of the clinical trial and processed during and after trial completion.

Personal data collected as part of the clinical trial will be transferred to/from the institution/investigator, LEO 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.

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

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

Appendix 4D: Record keeping, quality control, and data handling

Case report forms

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. Data recorded in the eCRFs will be accessible to the trial site and LEO personnel immediately after entry. The CRFs 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 CRFs 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

CRF 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.

Principles for data entry

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

If an abnormal finding (vital signs, physical examination, laboratory tests, ECG) at any other visit than the (first) screening visit is considered by the investigator to be clinically significant, it will be reported as an AE in accordance with Section 11.2. Further, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom or illness observed after screening will be reported as an AE in accordance with Section 11.2.

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 one 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.
- Subject ID.
- The fact that the subject is participating in a clinical trial in AD including treatment arms of tralokinumab or placebo for 52 weeks (68 weeks in selected countries).
- 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 perform ongoing source data verification to confirm that data entered into the CRF 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 study agreements, ICH GCP, and all applicable regulatory requirements.

The monitoring visit intervals will depend on the trial site's recruitment rate, the compliance of the trial site with the protocol and 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. LEO will assess all protocol deviations and decide if any of these deviations must be reported to the regulatory authorities as a serious breach of GCP and the protocol, as required by local legislation. Protocol deviations will be included 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.

Data handling

Subject data should be entered into the CRF as soon as possible after each visit in accordance with the requirements described in the Clinical Trial Agreement, if applicable. Queries for discrepant data will be generated automatically by the system upon entry or manually by the

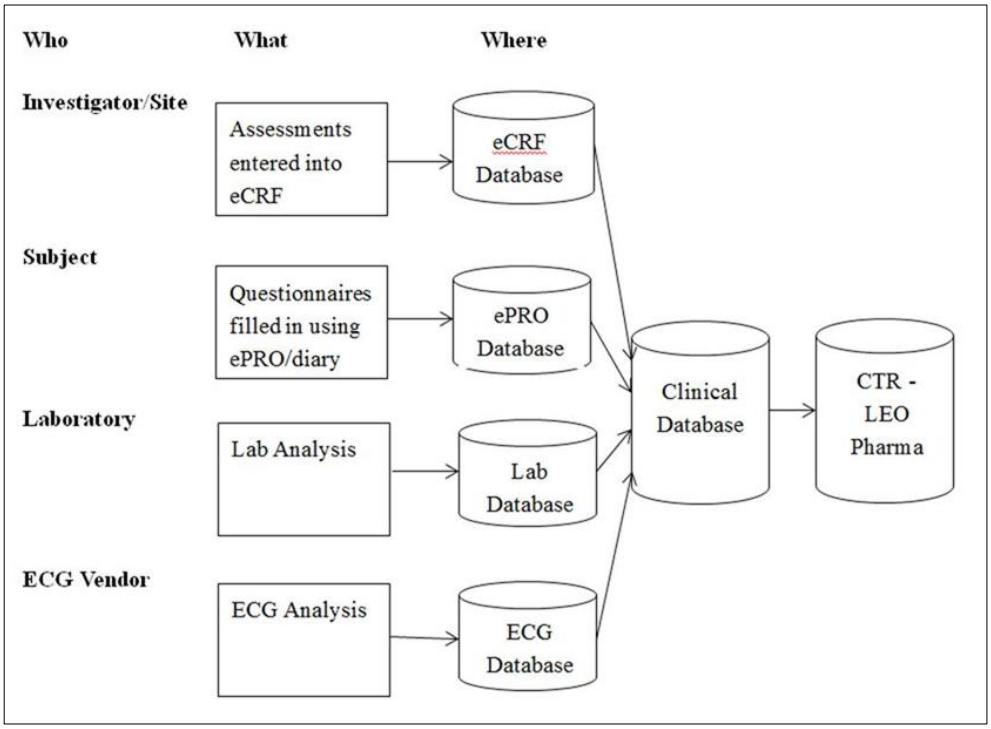
CRA, sponsor's medical expert, or the data manager. All queries will be raised electronically within the electronic data capture system. This systematic validation will ensure that a clean and consistent database is provided for the statistical analysis.

An electronic PRO (ePRO) solution will be used to capture patient-reported data (data from questionnaires completed at the trial site and eDiary data). By the use of an ePRO, data will be available immediately after data entry and available for 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 16.

Panel 16 Transmission of electronic data



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 (ICH E6, Guideline for Good Clinical Practice) 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 records may be destroyed during the retention period without the written approval of LEO. No records 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 a copy of the eCRFs and ePRO data for all 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 IEC/IRBs.

Appendix 4E: Registration, reporting and publication policy

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, latest 12 months after trial completion. 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.

In the case of a multi-centre trial the first publication will be a joint multi-centre publication. Multi-centre publications will be prepared in collaboration between LEO and the members of a writing group, which shall be appointed by LEO.

Publication by an investigator of his/her trial results shall not be made public before the first multi-centre publication.

If no multi-centre publication has been 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, 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 submitting or presenting a manuscript relating to the clinical trial to a publisher, reviewer or other outside person, the investigator shall provide to LEO a copy of all such manuscripts, and LEO shall have rights to review and comment. Upon the request of LEO, the investigator shall 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, delay the publication or presentation to allow LEO to protect its inventions and other intellectual property rights described in any such manuscripts. In case the first multi-centre publication is still ongoing and has not been made public at the time of notification, 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.

LEO complies with recommendations from the International Committee of Medical Journal Editors and 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) and Pharmaceutical Research and Manufacturers of America (PhRMA) on disclosure of information about clinical trials, trial results and authorship.

Appendix 4F: Insurance

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

Appendix 4G: 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 4H: Committee structure

Patient safety will be carefully assessed by an independent Data Monitoring Committee (DMC). All members will be independent of the trial (i.e. they will not be participating investigators or employees at participating sites) and of LEO (i.e. they will not be LEO employees). The DMC members are experienced with clinical trials and will be responsible for assessing the safety of the subjects through assessment of the safety of the treatment regimen during the trial and through monitoring the overall conduct of the trial. Refer to Appendix 8 for a list of trial committee members.

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

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

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

Appendix 4I: 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.
- Discontinuation of further IMP development.

Completion of trial

Investigators will be informed when subject recruitment is to cease. Trial enrolment 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 4J: Responsibilities

The international coordinating investigator (ICI) is responsible for the approval of the (consolidated) clinical trial protocol, including any amendment(s) and the CTR on behalf of all clinical trial investigators and as agreed to in an International Coordinating 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 5: Hanifin and Rajka (1980) diagnostic criteria for AD

From Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. 1980;92 (Suppl):44-47.

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 6: Guidance for anaphylaxis diagnosis

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-397.

The National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 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 (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, 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 (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   - Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   - Persistent gastrointestinal symptoms (eg, 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 7: Country-specific requirements

JAPAN

Section 6 Objectives and endpoints

In Japan, the maintenance endpoints of IGA 0/1 and EASI75 at Week 52 for subjects achieving clinical response at Week 16 are evaluated as primary maintenance endpoints. This regulatory requirement will have no impact on the analysis since an adjustment for multiplicity is implemented for these 2 endpoints. Please see Section 12.3.4 for details on the multiple testing procedure applied to control the overall type 1 error rate for the trial.

Section 8.2 Inclusion criteria - Inclusion criterion no. 1

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

In Japan, the legal representative must sign the informed consent if the subject is below 20 years of age.

Section 8.2 Inclusion criteria - Inclusion criterion no. 2

Age 18 and above.

In Japan, inclusion criterion no. 2 will be as follows: Japanese subjects aged 18 and above.

Section 9.9.3 Drug accountability

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

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

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

Trial sites which do not have such IMP destruction procedures in place will dispose used syringes in sharps bins which will be shipped to the contract manufacturing organisation (CMO).

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

Section 9.11 Reporting product complaints

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

Critical complaints (defined as any issue, defect, 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 Pharmacovigilance, LEO within 24 hours.

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

Fax number: +81 3 4243 3311

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

Note: reports sent to the above fax number and email address will automatically be forwarded to Global Pharmacovigilance, LEO.

Section 10.1 Overview

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

In Japan, investigators must be a dermatologist.

Section 11.3.1 Investigator reporting responsibilities

Any SAE must be reported to LEO on the (paper) SAE Form within 24 hours of first knowledge. The completed SAE form must be faxed or scanned and e-mailed to Global Pharmacovigilance, LEO.

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

Fax number: +81 3 4243 3311

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

Note: reports sent to the above fax number and email address will automatically be forwarded to Global Pharmacovigilance, LEO.

Section 11.3.2 LEO reporting responsibilities

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

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

Section 11.4.1 Pregnancy

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

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

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

Fax number: +81 3 4243 3311

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

Note: reports sent to the above fax number and email address will automatically be forwarded to Global Pharmacovigilance, LEO.

Appendix 4A: Regulatory and ethical considerations

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

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

Appendix 8: Contact list

Contact list of LEO, protocol authors, vendors, and trial committees

Contact details for the clinical project manager, national lead CRA (NLCRA), 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

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

LEO Pharma K.K.
3-11-6 Iwamotocho
Chiyoda-ku
Tokyo 101-0032
Japan

Protocol authors

Andreas Wollenberg, Prof. Dr. med. Dr. h.c., International coordinating investigator, Department of Dermatology and Allergy, Ludwig-Maximilian University Munich, Germany

PPD, M.Sc. Stat, Principal Statistician, LEO Pharma A/S, Denmark

PPD,, MD, Senior Global Medical Science Lead, LEO Pharma A/S, Denmark

PPD, PhD, Senior Principal Scientific Advisor, LEO Pharma A/S, Denmark

PPD, MD, Senior PV Advisor, LEO Pharma A/S, Denmark

PPD, M.Sc. Pharm, Clinical Project Manager, LEO Pharma A/S, Denmark

PPD, PhD, Medical Communication Scientist, LEO Pharma A/S, Denmark

CROs/vendors

Service	Name and address
Data management	Quanticate Ltd. Bevan House, 9-11 Bancroft Court, Hitchin, Hertfordshire SG5 1LH United Kingdom
ePRO	CRF Health Management Ltd. 3rd Floor, Brook House, 229-243 Shepherds Bush Road, Hammersmith, London W6 7AN United Kingdom
ECG	Cardiabase S.A.S. Villa Alsacienne, 78 Avenue du XXe Corps, 54000 Nancy France
Central Lab	ACM Global Central Laboratory 23 Hospital Fields Road, York YO10 4DZ United Kingdom
PK analysis and ADA	Covance Laboratories Ltd. Otley Road, Harrogate, North Yorkshire, HG3 IPY United Kingdom
Photography	Canfield Scientific, Inc. 253 Passaic Ave., Fairfield, NJ 07004 United States of America
IWRS	Quanticate Ltd. Bevan House, 9-11 Bancroft Court, Hitchin, Hertfordshire SG5 1LH United Kingdom
CMO	Almac Clinical Services Ltd. Almac House, 20 Seagoe Industrial Estate, Craigavon BT63 5QD, United Kingdom
CRO services in Japan	intellim Corporation 18F, Mainichi Intecio, 3-4-5 Umeda, Kita-ku, Osaka 530-0001 Japan
Emergency unblinding CRO	C3i, Inc. 25 Lindsley Drive, Morristown, NJ 07960 United States of America
Microbiology	AROS Applied Biotechnology A/S Palle Juul-Jensens Boulevard 82, DK-8200 Aarhus N Denmark

Service	Name and address
Biomarkers (IL-13, IL-17 and IL-22 serum analysis)	Eurofins Pharma Bioanalytics Services US Inc. 15 Research Park Drive, St. Charles, MO 63304 United States of America
Biomarkers (other serum biomarkers)	Eurofins Pharma Bioanalysis Services UK Ltd. 90 Park Drive, Milton Park, Abingdon, OX14 4RY United Kingdom
Skin biopsies (gene expression analysis)	AROS Applied Biotechnology A/S Palle Juul-Jensens Boulevard 82, DK-8200 Aarhus N Denmark

Trial committees

Data Monitoring Committee

Role	Name
Chairman	PPD, Dr. med. Dr. phil. Technical University of Munich, Germany
Member	PPD, MD University of Michigan, USA
Member	PPD, BSc MSc CStat CSci S-cubed Biometrics Ltd, UK

Appendix 9: WHO model prescribing information for classification of topical corticosteroids

Hydrocortisone and betamethasone are examples of low- and high-potency topical corticosteroids (TCS). TCS have been ranked in terms of potency into 4 groups consisting of 7 classes. Class I TCS are the most potent and Class VII TCS are the least potent (Panel 17). Efficacy and side-effects are greatest with the Class I ultra-high-potency preparations which should only be used for limited time periods (2–3 weeks).

Representative preparations by group are listed in the table below according to the WHO model prescribing information for drugs used in skin diseases (41). These groups may vary depending on the formulation and concentration and should be considered approximate. In general, ointments are more potent than creams or lotions. Potency is also increased when TCS are used under occlusive dressings or in intertriginous areas.

Panel 17 Classification of topical corticosteroids

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

Panel 17 Classification of topical corticosteroids (continued)

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

Source: WHO model prescribing information: drugs used in skin diseases (41).

Appendix 10: Protocol amendment history

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

Amendment 2 (12-Dec-2017)

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 reason for the amendment is due to a request for changes from the Health Authorities in the US after their review of the protocol.

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 number and name	**Description of change**	**Brief rationale**
Section 6.1 Trial objectives and endpoints: Initial treatment period of Weeks 0 to 16	EASI90 has been added as an additional secondary endpoint.	Added to further substantiate the clinical relevance of the treatment effect on the change from baseline to Week 16 in EASI score.
Section 6.1 Trial objectives and endpoints: Initial treatment period of Weeks 0 to 16	The following other objective has been added: To evaluate the efficacy over time of tralokinumab on severity and extent of AD, itch, and health-related quality of life compared with placebo.	Added to allow for an evaluation of the efficacy of tralokinumab over time on severity and extent of AD, itch, and health-related quality of life compared with placebo.
	The following endpoints have been added as other endpoints: • IGA 0/1 at each scheduled assessment until Week 14. • EASI75 at each scheduled assessment until Week 14. • Change in SCORAD from baseline to each scheduled assessment until Week 14. • Change from baseline to each week through Week 1 to 15 in Worst Daily Pruritus NRS (weekly average). • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to each week through Week 1 to 15. • Change in DLQI score from baseline to each scheduled assessment until Week 14.	Added to allow for an evaluation of the efficacy of tralokinumab over time on severity and extent of AD, itch, and health-related quality of life compared with placebo.
	The following other endpoints have been removed: • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to Week 2 • Change from baseline to Week 2 in Worst Daily Pruritus NRS (weekly average).	Removed because these 2 endpoints are covered by the new endpoints above (change from baseline to each week; reduction from baseline to each week).

Section number and name	**Description of change**	**Brief rationale**
Section 6.1 Trial objectives and endpoints: Initial treatment period of Weeks 0 to 16	The following endpoints have been added as other endpoints: • HADS anxiety and HADS depression scores <8 at Week 16 in subjects with baseline HADS anxiety or HADS depression subscale scores of ≥8. • Reduction from baseline to Week 16 of POEM of ≥4 points among subjects with baseline POEM ≥4.	To evaluate the patient-reported outcomes and health care resource utilisation.
Section 6.2 Trial objectives and endpoints: Maintenance treatment period of Week 16 to 52 for responders at Week 16	• IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 **achieved without rescue medication** after initial randomisation to tralokinumab. • EASI75 at Week 52 among subjects with EASI75 at Week 16 **achieved without rescue medication** after initial randomisation to tralokinumab. • IGA 0/1 or EASI75 at Week 52 among subjects with IGA 0/1 or EASI75 at Week 16 **achieved without rescue medication.** The maintenance endpoints of IGA 0/1 and EASI75 at Week 52 for subjects achieving clinical response at Week 16 **without rescue medication** are considered secondary endpoints. In Japan, the maintenance endpoints of IGA 0/1 and EASI75 at Week 52 for subjects achieving clinical response at Week 16 **without rescue medication** are evaluated as primary maintenance endpoints.	To evaluate the maintenance of effect achieved with tralokinumab.
Section 7.1 Overall trial design	A ~~16~~ **14**-week off treatment follow-up period for the assessment of safety is also included (Weeks 52 to 66). All subjects will complete a ~~16~~**14-**week off treatment follow-up period for the assessment of safety and ADA at Week 66 (or Week 82).	Clarification that the follow-up period has a duration of 14 weeks since the maintenance period and the open-label arm both include the Week 52 visit. Since the last dose of IMP is administered at Week 50 (or Week 66), the follow-up visit will occur 16 weeks after last IMP administration.

Section number and name	**Description of change**	**Brief rationale**
Section 7.1 Overall trial design	Transfer to open-label may occur at any visit while the subject is in the maintenance treatment period **but no earlier than Week 22**.	Clarification that transfer to open-label requires a persistent worsening of disease observed over 3 consecutive visits in the maintenance period.
Section 8.2 Inclusion criteria (no. 9)	Worst Daily Pruritus NRS 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)**.	Clarification of how Worst Daily Pruritus NRS at baseline will be calculated.
Inclusion criteria (no. 11)	The subjects must have used the contraceptive method continuously for at least 1 month prior to the pregnancy test **at baseline**.	Clarification that female subjects of childbearing potential must have used a highly effective form of birth control for at least 1 month prior to baseline.
Section 10.5.2.2 Small biomarker panel (all subjects)	All subjects will have blood samples taken for analysis of a small panel of biomarkers**. The biomarkers to be analysed include, but are not limited to, the following:** ~~(~~periostin, DPP4, CCL17 (also known as thymus and activation regulated chemokine [TARC]), IL-13, IL-17, IL-22, and beta-defensin 4A ~~[~~**(**DEFB4A~~]~~).	Clarification that the small biomarker panel may include more than 7 biomarkers.
Section 10.5.3 Skin biopsies (selected trial sites)	Histology/immunohistochemistry/in-situ hybridisation • T cells (e.g., CD3+ and CD8+), dendritic cells (e.g., CD11c+, FcεR1), monocytes/macrophages (e.g., CD68), ~~neutrophils (e.g., myeloperoxidase),~~ epidermal markers (e.g., epidermal thickness, keratin type I cytoskeletal 16, proliferation marker protein Ki 67, protein S100 A, filaggrin, loricrin).	Neutrophils will not be analysed because neutrophil levels are not expected to change.
Section 11.5.6 Aggravation of condition	Any clinically significant aggravation/ exacerbation/worsening of any medical condition(s), compared to ~~baseline~~ **screening**, must be reported as an AE.	Clarification that AE reporting starts at screening, not baseline. This is in alignment with the information given in Section 11.1 and Appendix 4D.

Section number and name	Description of change	Brief rationale
Section 12.2 Trial analysis sets	A per protocol analysis set will be used as an efficacy subset for the analysis of the **primary** endpoints up to Week 16 (visit 12) The per protocol analysis set will be defined by excluding subjects from the full analysis set for whom any of the following conditions apply: • receive no treatment with the IMP. • provide no ~~efficacy data~~ **assessment of IGA or EASI** following start of treatment. • are known to have taken the wrong IMP throughout the initial treatment period of the trial. • do not fulfil **all** the ~~disease defining inclusion criterion (i.e. inclusion criterion no. 3)~~ **inclusion criteria no. 3, 6, 7 and 8**. ~~Further exclusion of subjects or subject data will be decided upon after a blinded review of the data, reviewing all the remaining in- and exclusion criteria, but focusing on concomitant medication that may affect AD and also considering compliance/adherence and violations of visit windows.~~	Specification that the per protocol analysis set will be used for analysis of the primary endpoints only. To predefine the criteria leading to exclusion from the per protocol analysis set, rather than deferring until a blinded review of the data.
Section 12.3.1 Disposition of subjects	For all randomised subjects the reasons for **permanent discontinuation of IMP and for** leaving the trial in the initial treatment period will be presented by last visit attended and by treatment group. For the subjects in the maintenance safety analysis set, the reasons for **permanent discontinuation of IMP and for** leaving the trial or treatment arm will be presented by last visit attended and by the assigned treatment group at Week 16. For the subjects in the open-label safety analysis set, the reasons for **permanent discontinuation of IMP and for** leaving the trial will be presented by last visit attended.	Clarification that reasons for permanent discontinuation of IMP will be presented.

Section number and name	**Description of change**	**Brief rationale**
Section 12.3.2 Demographics and other baseline characteristics	The presentations will be overall and by treatment group. Presentations of age, sex, ethnicity, race, baseline disease severity, and Worst Daily Pruritus NRS weekly average at baseline will also be given by region **and by baseline disease severity (IGA 3 or 4).**	Baseline disease severity added since this is also a stratification factor, in addition to region.
Section 12.3.5.1 Analysis of primary endpoints	This section has been amended to implement the concept of estimands together with the pre-specification of sensitivity analyses. The primary analyses of the primary endpoints are unchanged compared to the statistical analysis plan provided in the original protocol dated 03-Mar-2017.	To pre-specify the method of handling missing data.
Section 12.3.5.2 Analysis of secondary endpoints	This section has been amended to implement the concept of estimands together with the pre-specification of sensitivity analyses. The primary analyses of the secondary endpoints are unchanged compared to the statistical analysis plan provided in the original protocol dated 03-Mar-2017.	To pre-specify the method of handling missing data.
Section 12.3.5.3 Analysis of additional secondary endpoints	This section has been updated to describe the statistical analysis of the additional secondary endpoint EASI90.	To describe the statistical analysis of new endpoint.
Section 12.3.5.4.1 Efficacy over time	This is a new section describing the statistical analysis of the 6 new other endpoints which address efficacy over time.	To describe the statistical analysis of new endpoints.

Section number and name	Description of change	Brief rationale
Section 12.3.5.4.2 Patient-reported outcomes	This section has been updated to include a description of the statistical analysis of the following 2 new other endpoints: • HADS anxiety and HADS depression scores <8 at Week 16 in subjects with baseline HADS anxiety or HADS depression subscale scores of ≥8 • Reduction from baseline to Week 16 of POEM of ≥4 points among subjects with baseline POEM ≥4.	To describe the statistical analysis of new endpoints.
	The description of the analysis of the following 2 endpoints have been removed from this section: • Reduction of at least 4 from baseline to Week 2 in Worst Daily Pruritus NRS weekly average • Change from baseline to Week 2 in Worst Daily Pruritus NRS weekly average.	The analysis of these endpoints is now covered by the new section 12.3.5.4.1.
	For the PGI-B, a day of 'no or slight bother' is defined as answering the question with 'not at all' or 'slightly'. The subjects' number of days of 'no or slight bother' will be tabulated per treatment group for the initial treatment period. The mean number of days will be presented with 95% CIs and compared between the 2 treatment groups using an analysis of variance model including treatment, region, and baseline IGA as factors. **In this analysis, data collected after permanent discontinuation of IMP or after initiation of rescue medication will be disregarded.**	Clarification regarding data collected after permanent discontinuation of IMP or after initiation of rescue medication, to align with the primary estimand for the continuous secondary endpoints.

Section number and name	**Description of change**	**Brief rationale**
Section 12.3.6.1 Analysis of maintenance endpoints	The main changes are as follows: • An estimand framework has been introduced for the analysis of the maintenance endpoints. The primary analysis provided in the statistical analysis plan in the original protocol dated 03-Mar-2017 is unchanged. • Clarification has been added on the analysis set for the maintenance endpoints IGA of 0/1 at Week 52 and EASI75 at Week 52. • The sensitivity analysis allowing TCS treatment under certain conditions has been removed (mild to moderate strengths [WHO classification] TCS, on ≤250 cm2 affected BSA, for ≤5 consecutive days, not more often than every 4 weeks, ≤3 courses from Week 16 to Week 50 and last course is completed prior to the Week 50 visit, allowing at least a 2-week washout prior to the Week 52 assessment). • An LOCF sensitivity analysis has been introduced.	To conduct a sensitivity analysis which is similar to the sensitivity analysis no. 2 for the primary estimand for the primary endpoints. The sensitivity analysis described in the original protocol – which allowed TCS under certain conditions – is inconsistent with the rescue medication algorithm applied in the initial treatment period.
Section 12.3.6.2.1 Time to relapse	Initiation of rescue medication is now considered an event of relapse, rather than a censoring of the time to relapse. A clarification has been added that only subjects who achieve response at Week 16 without rescue medication will be included in the analysis. Clarification that the log-rank test will be stratified by region and that this test is considered a supplementary exploratory analysis.	Initiation of rescue medication is unlikely to be independent of the time to relapse, hence it is not considered appropriate to consider it a censoring event. The log-rank test will be stratified according to region, to align with the analysis of the binary maintenance endpoints. Clarification that the log-rank test is considered a supplementary exploratory analysis.

Section number and name	**Description of change**	**Brief rationale**
Section 12.3.6.2.3 Supportive maintenance	To support the maintenance objective, the response IGA 0/1 or EASI75 at Week 52 will be presented and analysed **as described above for the primary analysis of the maintenance estimand** for ~~all~~ subjects in the maintenance analysis set **who did not receive rescue medication prior to Week 16** ~~The estimated response rates and corresponding 95% CIs, and the pairwise treatment differences will be presented~~.	To clarify that only subjects who achieve response at Week 16 without rescue medication will be included in the analysis.
Section 12.3.9 Analysis of data per last subject's Week 52 visit	This is a new section which specifies that the trial will be unblinded once all randomised subjects have completed the Week 52 visit. All pre-specified analyses related to the initial and maintenance treatment period will be based on the data cut-off date of the last subject's Week 52 visit.	To support submission for regulatory approval.
Appendix 1 Protocol summary	Updated with the changes described above, as applicable.	To reflect updated text in protocol.
Appendix 4B Informed consent process	Subjects must be re-consented to the most current version of the ICF(s) during their participation in the trial, **if required**.	Clarification that subjects will only be re-consented to a new version of the ICF(s), if deemed necessary.
Appendix 4H Committee structure	Refer to Appendix 8 for ~~contact details on all~~ **a list of** trial committee members.	As the DMC has been established, the list of committee members has been included; however, contact details are not provided in the protocol.
Appendix 8 Contact list	Members of the DMC have been listed.	DMC has now been contracted.
Throughout	Minor editorial and document formatting revisions.	Minor, have therefore not been summarised.

Amendment 1 (28-Aug-2017)

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 reason for the amendment is due to a request for changes from the Health Authorities in Europe after their review of the protocol.

Note: In the table below, text added to the protocol is written in **bold** and deleted text has a ~~line through it~~.

Section number and name	Description of change	Brief rationale
Section 2 Trial identification	**ClinicalTrials.gov number: NCT03131648**	ClinicalTrials.gov identifier received and it has therefore been added.
Section 3 Schematic of trial design Section 4 Schedule of procedures Section 7.1 Overall trial design Section 7.3 End of trial definition	All subjects in the trial will have a safety follow-up visit (end of trial visit) 16 weeks after last injection of IMP, including those that are offered participation in the long-term extension trial conducted under a separate protocol (LP0162-1337). Details regarding enrolment of subjects into the long-term extension have been removed.	To ensure that safety follow-up information is collected for all subjects enrolled in this trial, and to ensure that a safety evaluation can be made based on data collected after IMP has been discontinued. Furthermore, the evaluation of anti-drug antibodies is considered to be most reliable when samples are taken in the absence of IMP. Details regarding enrolment of subjects into trial LP0162-1337 will be described in the protocol for LP0162-1337.
Section 4 Schedule of procedures	2 blood samples (PK and anti-drug antibodies) have been added at Week 4 (visit 5).	To better monitor potential development of immunogenicity.

Section number and name	Description of change	Brief rationale
Section 4 Schedule of procedures Section 7.1 Overall trial design Appendix 1 Protocol summary	The criteria for transfer to open-label treatment have been changed: ~~(i) Persistent IGA of 2 and not achieving EASI75 over at least a 4-week period (i.e., subjects must have IGA of 2 and not achieve EASI75 at 3 consecutive visits).~~ ~~(ii) On a single occasion, an IGA of at least 3 and not achieving EASI75.~~ ~~(iii) On a single occasion not achieving EASI50 with an IGA of at least 2.~~ **Subjects with IGA=0 at Week 16: IGA of at least 2 and not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits).** **Subjects with IGA=1 at Week 16: IGA of at least 3 and not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits).** **Subjects with IGA >1 at Week 16: Not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits).**	To keep subjects who entered maintenance treatment with IGA 0/1 in maintenance treatment until they have a sustained 2-step change in IGA (IGA of 0 becoming ≥2; IGA of 1 becoming ≥3).
Section 4 Schedule of procedures Section 7.1 Overall trial design Section 8.2 Inclusion criteria Section 9.4 Background treatment (emollients) Appendix 1 Protocol summary	All subjects must use an emollient twice daily **(or more, as needed)**	Clarification that the use of background treatment (emollients) is <u>at least</u> twice daily or more, as needed. This change has been implemented throughout the document.

Section number and name	**Description of change**	**Brief rationale**
Section 4 Schedule of procedures Section 7.1 Overall trial design	The following text has been added to footnote no. 1 in Panel 2: **Similarly, for subjects who only require a 2-week wash out, screening visits 1 and 2 will be combined (Week -2).** In Section 7.1, the following text has been added under Screening period: **Similarly, if only a 2-week wash-out is required, screening visits 1 and 2 will be combined (Week -2; visit 2).**	Specification that the 2 screening visits (visits 1 and 2) will be combined for subjects who only require a 2-week wash-out.
Section 5.1 Atopic dermatitis	Treatment recommendations for AD include topical therapies, the main being topical corticosteroids (TCS). Unfortunately, TCS **and topical calcineurin inhibitors (TCIs)** have limited efficacy in patients with moderate to severe disease. TCS and **non-biologic** ~~other treatment options like topical calcineurin inhibitors (TCI) and~~ systemic therapies are all associated with toxicities with long-term use (6-8).	Corrections as no toxicities have been reported with long-term treatment with TCIs.
Section 5.5 Benefit/risk assessment	A number of theoretical potential risks have been identified that are described in the current Investigator's Brochure, including hypersensitivity reactions, ~~infusion reactions,~~ immune complex disease, ~~and~~ severe infections**, malignancies, and interference with reproductive function**	Infusion reactions have been deleted from the list since they are not relevant for this trial. Malignancies and interference with reproductive function added to align with the Investigator's Brochure.
Section 8.3 Exclusion criteria	10. Receipt of any marketed (i.e. immunoglobulin, anti-IgE) or investigational biologic agent, **including dupilumab** 18. History of anaphylaxis **following any biologic therapy**.	Dupilumab is now approved in USA, and has therefore been added to exclusion criterion no. 10. Clarification on which kind of previous anaphylaxis will lead to exclusion. A large proportion of subjects with moderate to severe AD will have had food allergies and other allergies during childhood, manifested as anaphylaxis, with no relevance for later risk of anaphylactic reactions to tralokinumab.

Section number and name	Description of change	Brief rationale
Section 8.5 Discontinuation Section 4 Schedule of procedures	Subjects who permanently discontinue ~~treatment~~ **IMP** for any reason **will be asked to attend an early termination visit and return to the trial site for 1 or 2 additional visits as indicated below depending on the time of discontinuation of IMP** ~~should attend an early termination visit and a safety follow-up visit 16 weeks after last administration of IMP~~ (see the SoP [Section 4] for data to be collected at these visits). The investigator will review any AEs which will be followed up according to Section 11.6, if the subject agrees. **Subjects who permanently discontinue IMP prior to Week 16 will be asked to attend:** • **Early termination visit.** • **Nominal Week 16 visit (16 weeks after randomisation).** • **Safety follow-up visit (16 weeks after last administration of IMP).** **Subjects who discontinue IMP at Week 16 or after Week 16 will be asked to attend:** • **Early termination visit.** • **Safety follow-up visit (16 weeks after last administration of IMP).** If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site's trial records. Reason(s) for discontinuation **from IMP and withdrawal from the trial** must be recorded in the medical records	Clarification that subjects who permanently discontinue IMP prior to Week 16 should also be assessed at the nominal Week 16 visit. This will allow sensitivity analyses of primary endpoints and secondary endpoints in the initial treatment period.

Section number and name	Description of change	Brief rationale
Section 9.3.2 Emergency unblinding of individual subject treatment	An emergency unblinding request can be made by the investigators, ~~other~~ 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 ~~requester~~ **investigator** can unblind a subject's treatment in the IWRS. For a requester **who is not a member of the trial staff and who does** not ~~without~~ have access to the IWRS (e.g., ~~an HCP not involved in the trial~~ **a physician at an emergency room**), a local contact number for the **emergency** unblinding CRO is provided **on the subject card (see Appendix 4B) to be used if the investigator or delegated site staff cannot be reached.**	Clarification regarding the procedure for emergency unblinding of the individual subject's treatment.
	Emergency unblinding CRO	Clarification throughout the section that the unblinding CRO is to be used for emergency unblinding only.
Section 9.11 Reporting product complaints Appendix 7 Country-specific requirements (Japan)	Any defects **or issues** with the IMP **as well as any** device **deficiency (including malfunctions, use errors, and inadequate labelling)** must be reported to Global Pharmacovigilance, LEO on the **trial-specific** (paper) ~~Device~~ Complaint Form within 3 days of first knowledge. **Critical complaints (defined as any issue, defect, 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 Pharmacovigilance, LEO within 24 hours.**	Clarification that product complaints related to the IMP itself must also be reported as product complaints. Clarification that any device deficiency must be reported as a product complaint. Clarification that critical complaints are subject to expedited reporting. Clarification that adverse events in connection with product complaints are to be reported as adverse events or serious adverse events as appropriate.

Section number and name	Description of change	Brief rationale
	~~This report~~ **Complaint forms** should contain a detailed description of the **defect, issue, or** ~~malfunction~~ **device deficiency**, including whether **it** ~~the malfunction~~ 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 11.2 and 11.3.**	
Section 10.1 Overview	Investigator assessments (performed only by adequately trained investigators; the same investigator should perform all the evaluations for a given subject throughout the entire trial period) **in the following order:** **1. SCORAD component C, then component A and B.** **2. IGA.** 3. **EASI.**	Clarification that SCORAD component C (completed by the subject) will be completed prior to any investigator assessments.
Section 10.3.1.1 Investigator's Global Assessment	Clinical signs and morphological descriptors have been added to the IGA scale in Panel 10.	Added following a request from the FDA.
Section 10.3.1.2 Eczema Area and Severity Index	Footnote added to Panel 12 on the EASI severity score scale: **Half-points (0.5; 1.5; 2.5) may also be used.**	Clarification that the EASI severity score scale also includes half-points (in alignment with the eCRF and the trial manual).
Sections 10.3.2.1 Eczema related Sleep numeric rating scale to 10.3.2.12 Treatment Satisfaction Questionnaire for Medicine	All 12 questionnaires are provided in the investigator trial file and not in a trial manual.	Clarification on where questionnaires are filed.
Section 10.4.5 Laboratory testing	The central laboratory will provide results **in conventional units to trial sites in the US and in SI units to trial sites in Europe and Asia;** ~~the trial sites in the units preferred by the trial sites while~~ the results that are transferred to the trial database will ~~always~~ be in **conventional and** SI units.	Clarification regarding the units of the results from the clinical laboratory assessments provided to the trial sites across regions. Clarification that results transferred to the trial database will be in both conventional and SI units.

Section number and name	Description of change	Brief rationale
Section 10.4.7 Anti-drug antibodies measurements	**Samples will be retained for as long as the quality of the material permits evaluation but for no longer than 15 years after marketing authorisation.**	Clarification regarding storage of ADA samples.
Section 10.5.1.2 Staphylococcus aureus colonisation	~~To minimise the variation between trial sites, a traditional culture-based non-quantitative method for determining~~ S. aureus colonisation will be **determined** ~~used~~**using an RNA-based method (quantitative real-time polymerase chain reaction)**.	The RNA-based method is more reliable than the culture-based method when swabs have been frozen.
Section 10.6 Estimate of total blood volume collected	Total volume of blood to be withdrawn has been changed from 420 mL to 435 mL	2 blood samples (PK and anti-drug antibodies) have been added at Week 4
Section 11.4.1 Pregnancy	Pregnant subjects must **permanently** discontinue ~~from the trial~~ **IMP (see Section 9.8.1).**	Alignment between Sections 9.8.1 and 11.4.1.

Section number and name	Description of change	Brief rationale
Section 11.5.1 Adverse events of special interest	Malignancies diagnosed after randomisation, **excluding basal cell carcinoma, localised squamous cell carcinoma of the skin, and carcinoma in situ of the cervix** **Conjunctivitis, keratoconjunctivitis, and keratitis** added as adverse events of special interest. The additional information about these events that the investigators will provide to LEO is also included in Panel 14.	Basal cell carcinoma, localised squamous cell carcinoma of the skin, and carcinoma in situ of the cervix will be reported on standard AE forms as no additional information (e.g., histology report, oncology assessment, treatments) regarding these conditions need to be reported. These event types are common in the target population and should be monitored closely as per request from the authorities.
Section 11.7 Handling of an urgent safety measure	LEO must act immediately upon receipt of the urgent safety measure notification in accordance with ~~the~~ internal procedures **and local legislation**.	Clarification that the handling of urgent safety measures will be in accordance with local legislation.
Section 12.3.6.1 Analysis of maintenance endpoints	**The pooled analyses will only be presented in marketing authorisation applications**	Clarification that the pooled analyses of data from LP0162-1325 and LP0162-1326 will be presented in marketing authorisation applications.
Section 12.3.7.1 Adverse events	An overall summary of the **number of treatment-emergent AEs,** number (percentage) of subjects with any treatment-emergent AEs, SAEs, **deaths**, premature discontinuations from the trial due to AEs, treatment-related AEs and severe AEs will be presented.	Number of treatment-emergent AEs and deaths added to comply with ClinicalTrials.gov reporting requirements.

Section number and name	Description of change	Brief rationale
Appendix 4 B Informed consent process	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 IWRS cannot be performed.**	Clarification that the subject card also includes emergency numbers for emergency unblinding by the investigator and the emergency unblinding CRO (as also clarified in Section 9.3.2).
Appendix 4D Record keeping, quality control, and data handling	Protocol deviations will be documented and notified to the investigator. **LEO will assess all protocol deviations and decide if any of these deviations must be reported to the regulatory authorities as a serious breach of GCP and the protocol, as required by local legislation. Protocol deviations will be included in the CTR.** ~~Protocol deviations will be assessed by LEO and included in the CTR.~~	Clarification that it will be evaluated whether protocol deviations (non-compliances) must be reported to the regulatory authorities as a serious breach of GCP and the protocol.
Appendix 8 Contact list	Update of the protocol authors.	Due to change in the responsibilities of the sponsor's personnel.
	Emergency unblinding CRO	The name and address for the emergency unblinding CRO has been added.
	Microbiology	The name and address for the laboratory responsible for analysing skin swab data has been added.
	Biomarkers	The name and address for the 2 laboratories responsible for serum biomarker analysis has been added.
	Skin biopsies	The name and address for the laboratory responsible for gene expression analysis has been added.

Section number and name	**Description of change**	**Brief rationale**
Appendix 9 WHO model prescribing information for classification of topical corticosteroids	New appendix	Guidance for the investigators regarding the classification of topical corticosteroids as well as examples have been added to the protocol. In Section 9.7 (Rescue treatment), a cross reference to Appendix 9 has also been added.
Throughout	Minor editorial and document formatting revisions	Minor, have therefore not been summarised.

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