Cover Page

Official title: Tralokinumab in combination with topical corticosteroids for moderate to severe atopic dermatitis ECZTRA 3 (ECZema TRAlokinumab trial no. 3)
LEO Pharma number: LP0162-1339
NCT number: NCT03363854
Date: 29-Aug-2018

Updated Clinical Trial Protocol

LP0162-1339
Tralokinumab in combination with topical corticosteroids for moderate-to-severe atopic dermatitis
ECZTRA 3 (ECZema TRAlokinumab trial no. 3)

Phase 3 - Efficacy and safety trial

A randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab in combination with topical corticosteroids in 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 requirements.

LEO Pharma A/S	**Trial ID:**	**LP0162-1339**
	Date:	**29-Aug-2018**
	EudraCT No:	**2017-002065-21**
	Version:	**4.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

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

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

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:

Associate Professor Jonathan Silverberg, MD, PhD, MPH
International coordinating investigator

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

Document	Date	Type of protocol amendment
Amendment 3 (substantial)	29-Aug-2018	Global
Amendment 2 (substantial)	10-Apr-2018	Global
Amendment 1 (non-substantial)	15-Dec-2017	Global
Original protocol	04-Oct-2017	NA

Amendment 3 (29-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.

Overall rationale for the amendment

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

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

Note: The table below describes the changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has a ~~line through it~~).

Section no. and name	**Description of change**	**Brief rationale**
Clinical trial protocol statements Section 1 Protocol synopsis Appendix 6 Contact list	Professor PPD is replaced by Associate Professor Jonathan Silverberg.	As a new international coordinating investigator was appointed for this trial.
Section 1 Protocol synopsis Section 4 Schedule of procedures Panel 3 (footnote 1) Section 7.1 Overall trial design Section 7.3 End of trial definition Section 9.9 Provision for subject care following trial completion	Subjects will have a final safety follow-up visit 16 weeks after the last dose of IMP (which is also considered end of trial visit), except subjects who enter the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]). The subjects may enter ECZTEND at any time during the off-treatment safety follow-up period. For these subjects, the end of trial visit will be the last visit in the present trial. The subjects entering ECZTEND after completion of the end of treatment visit (Week 32) 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 the present trial may continue into the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]) without completing the safety follow-up period.

Section no. and name	Description of change	Brief rationale
Section 6 Trial objectives and endpoints	The following endpoints are added in Panel 4 under Other endpoints: • **Reduction from baseline to Week 16 of POEM score ≥4 points in subjects with baseline POEM score ≥4.** • **HADS anxiety and HADS depression subscale scores <8 at Week 16 in subjects with baseline HADS anxiety or HADS depression subscale scores ≥8.**	To allow for a further evaluation of the efficacy of tralokinumab+topical corticosteroids (TCS) on patient reported outcomes compared with placebo+TCS.
Section 9.8.2.1 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 temperature of IMP will be monitored.
Section 9.8.2.2 Storage of NIMP	The NIMP must be stored at room temperature at the site according to the approved **local** label for mometasone furoate ~~(Canada: 15-30°C; Europe: < 25°C; US: at 25°C [excursions to 15-30°C permitted])~~. 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 ensure that the NIMP will be stored at the trial site according to the approved local label and clarify that the storage temperature of NIMP will be monitored.

Section no. and name	Description of change	Brief rationale
Section 9.8.3.1 IMP 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 CMO ~~at the end of the trial~~. **For more information about IMP accountability, please refer to the IMP handling 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 10.3.2.9 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 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 (ICF) until completion of the clinical trial (defined as the safety follow-up visit 16 weeks after last injection of IMP). **For subjects entering the long-term extension trial (LP0162-1337, ECZTEND), any (S)AE with onset before the final visit in LP0162-1339 should be reported in LP0162-1339. If ongoing, the (S)AE will also be recorded as medical history in ECZTEND**.	To clarify how (S)AEs occurring in subjects entering LP0162-1337 (ECZTEND) will be collected if visits in LP0162-1339 overlap with visits in ECZTEND.

Section no. and name	Description of change	Brief rationale
Section 11.5.1 Adverse events of special interest Panel 10	The text in the heading of the right column was modified as follows: Additional information to be provided **(if available[1])** A footnote was added: **[1]The additional data to be recorded in the eCRF are not a requirement, but are to be reported by the investigator, if available, for example as part of standard clinical practice.**	To clarify that additional information is to be provided only if available and is not requirement.
Section 12.3.8.2 Patient-reported outcomes	The following text is added: **In the subgroup of subjects with either HADS anxiety or HADS depression subscale score ≥8 at baseline, the proportion of subjects with both HADS anxiety 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 ≥4, the proportion of subjects with a reduction in POEM score ≥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.**	To describe the statistical analyses of the new endpoints.
Section 12.3.9.1 Adverse events	SAEs and AESIs will be evaluated separately**.** ~~and a~~**A** narrative for each **SAE** will be given. **AESIs and** AEs leading to withdrawal from trial or permanent discontinuation of IMP will be **tabulated and** listed.	Tabulation and listings are considered a more practical and informative way of presenting AESIs. This will enable easier overview of the individual cases as well as sorting and pooling of data from other trials.

Section no. and name	Description of change	Brief rationale
Section 12.3.9.5 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 from the nAB assay will not be available.
Appendix 6 Contact list	LEO Pharma protocol authors are omitted.	To comply with the European General Data Protection Regulation.
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
AST	aspartate aminotransferase
BP	blood pressure
BSA	body surface area
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
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
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HCP	healthcare professional
HRQoL	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
IgG4	immunoglobulin G4
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
PK	pharmacokinetics
nAB	neutralising antibodies
NIMP	non-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
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
SCORAD75	at least 75% reduction in SCORAD score
TCI	topical calcineurin inhibitor(s)
TCS	topical corticosteroid(s)
Th2	T-helper-2
ULN	upper limit of normal (range)
UV	ultraviolet

1 Protocol synopsis

Trial ID EudraCT no. NCT no.	LP0162-1339 2017-002065-21 03363854
Title of trial	ECZTRA 3 (ECZema TRAlokinumab trial no. 3) A randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab in combination with topical corticosteroids (TCS) in subjects with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic therapy.
Short title	Tralokinumab in combination with TCS for moderate-to-severe AD.
Main objectives	Primary objective: To demonstrate that tralokinumab in combination with TCS is superior to placebo in combination with TCS in treating moderate-to-severe AD. Secondary objectives: To evaluate the efficacy of tralokinumab in combination with TCS on severity and extent of AD, itch, and health-related quality of life compared with placebo in combination with TCS. To assess safety of tralokinumab in combination with TCS when used to treat moderate-to-severe AD for 32 weeks.
Primary endpoints	• Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) at Week 16. • At least 75% reduction in Eczema Area and Severity Index (EASI) score from baseline (EASI75) at Week 16.
Secondary endpoints	• Change in Scoring Atopic Dermatitis (SCORAD) from baseline to Week 16. • Reduction of Worst Daily Pruritus numeric rating scale (NRS) (weekly average) of at least 4 from baseline to Week 16. • Change in Dermatology Life Quality Index (DLQI) from baseline to Week 16.
Trial design	The trial will consist of a screening period of 2 to 6 weeks (Weeks -6/-2 to 0), an initial treatment period of 16 weeks (Weeks 0 to 16), a continuation treatment period of 16 weeks (Weeks 16 to 32), and a 14-week off-treatment follow-up period for the assessment of safety (Weeks 32 to 46). Subjects will be randomised in a 2:1 ratio to receive multiple subcutaneous (SC) doses of tralokinumab (300 mg) or placebo every 2 weeks (Q2W) following a loading dose of 600 mg on Day 0 (or 4 mL placebo). Randomisation will be stratified by region and baseline disease severity. At Week 16, subjects will continue into continuation treatment until Week 32 (the last dose of investigational medicinal product [IMP] will be given at Week 30). The treatment during the continuation treatment period will depend on the regimen received in the initial treatment period and on the subject's clinical response at Week 16 (defined as IGA of 0 or 1 on a 5-point scale ranging from 0 [clear] to 4 [severe], or EASI75).

	Subjects randomised to tralokinumab in the initial treatment period and with a clinical response at Week 16 will be re-randomised 1:1 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). Subjects randomised to placebo in the initial treatment period and with a clinical response at Week 16 will receive placebo Q2W in the continuation treatment period. Non-responders at Week 16 in the tralokinumab and placebo groups will receive tralokinumab 300 mg Q2W. The primary endpoints are assessed at Week 16, and the final efficacy assessment will be conducted at Week 32. Starting on Day 0 (baseline), all subjects will be allowed to initiate treatment once daily with a supplied TCS on lesional skin and continue as needed throughout the treatment period. TCS use will be monitored throughout the trial. All subjects will use an emollient twice daily (or more, as needed) for at least 14 days before randomisation and will continue this treatment throughout the trial (including safety follow-up). On lesional skin, emollients should only be applied at a time where TCS is not applied; on TCS-untreated areas, the emollients may be applied at all times.
Main assessments	<u>Efficacy: investigator assessments</u> • IGA. • EASI. • SCORAD. • AD flares. <u>Efficacy: subject assessments</u> Six patient-reported outcomes (PROs) will be assessed daily using an electronic diary: Eczema-related Sleep NRS, Worst Daily Pruritus NRS, Average Daily Pruritus NRS, Patient Days of Topical Treatment Use, Patient Global Impression of Bother (PGI-B), and Patient Global Impression of Severity (PGI-S). Four PROs will be completed by the subjects at the site during trial visits: Patient Oriented Eczema Measure (POEM), DLQI, EuroQoL 5-Dimension Health Questionnaire 5 Level (EQ-5D-5L), and Hospital Anxiety and Depression Scale (HADS). <u>Safety assessments</u> Vital signs, physical examination, electrocardiograms, laboratory testing, pharmacokinetics, anti-drug antibodies, and adverse event reporting.
Main criteria for inclusion	• Age 18 and above. • Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD. • History of AD for ≥1 year.

	• Subjects who have a recent history of inadequate response to treatment with topical medications. • 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 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	• Subjects for whom TCSs are medically inadvisable e.g., due to important side effects or safety risks in the opinion of the investigator. • Active dermatologic conditions that may confound the diagnosis of AD. • Use of tanning beds or phototherapy within 6 weeks prior to randomisation. • Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomisation. • Treatment with TCS, TCI, or topical phosphodiesterase 4 (PDE-4) inhibitor within 2 weeks prior to randomisation. • Receipt of any marketed biological therapy (i.e. immunoglobulin, anti-immunoglobulin E) including dupilumab or investigational biologic agents. • Active skin infection within 1 week prior to randomisation. • Clinically significant infection within 4 weeks prior to randomisation. • A helminth parasitic infection within 6 months prior to the date informed consent is obtained. • Tuberculosis requiring treatment within the 12 months prior to screening. • Known primary immunodeficiency disorder.
Investigational medicinal products	<u>Tralokinumab (human recombinant IL 13 monoclonal antibody)</u> 150 mg/mL solution for 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.
Non-investigational medicinal product	<u>TCS (Europe: Class 3 [potent]; US: Class 4 [mid-strength])</u> Mometasone furoate, 0.1% cream provided in kit sizes of 180–225 g every 2 weeks.

Duration of treatment	Each subject's trial participation will be up to approximately 52 weeks: screening period (including wash-out, if applicable) up to 6 weeks, treatment period of 32 weeks, and 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).
Number of subjects to be enrolled	A total of 369 subjects will be randomised 2:1 to treatment (246 subjects to tralokinumab; 123 subjects to placebo).
Number and distribution of trial sites	Approximately 70 sites in Europe and North America.
Statistical methods	<u>Primary endpoints</u> The difference in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity. Subjects with missing data or subjects who receive rescue medication prior to the Week 16 visit will be considered as non-responders in the analysis. 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. <u>Secondary endpoints</u> The change from baseline to Week 16 in SCORAD will be analysed using a repeated measurements model on the post baseline responses up to Week 16. Reduction of Worst Daily Pruritus NRS weekly average of at least 4 from baseline to Week 16 is a binary endpoint, and as such it will be analysed as described for the primary endpoints. Change from baseline to Week 16 in DLQI will be analysed the same way as change in SCORAD. The secondary endpoints will be tested using the Holm method for multiplicity adjustment hereby controlling the overall type 1 error rate for the trial.
International coordinating investigator	Associate Professor Jonathan Silverberg, MD, PhD, MPH, Departments of Dermatology, Preventive Medicine and Medical Social Sciences, Northwestern University Feinberg School of Medicine, United States.
Sponsor's name/ address	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

2 Trial identification

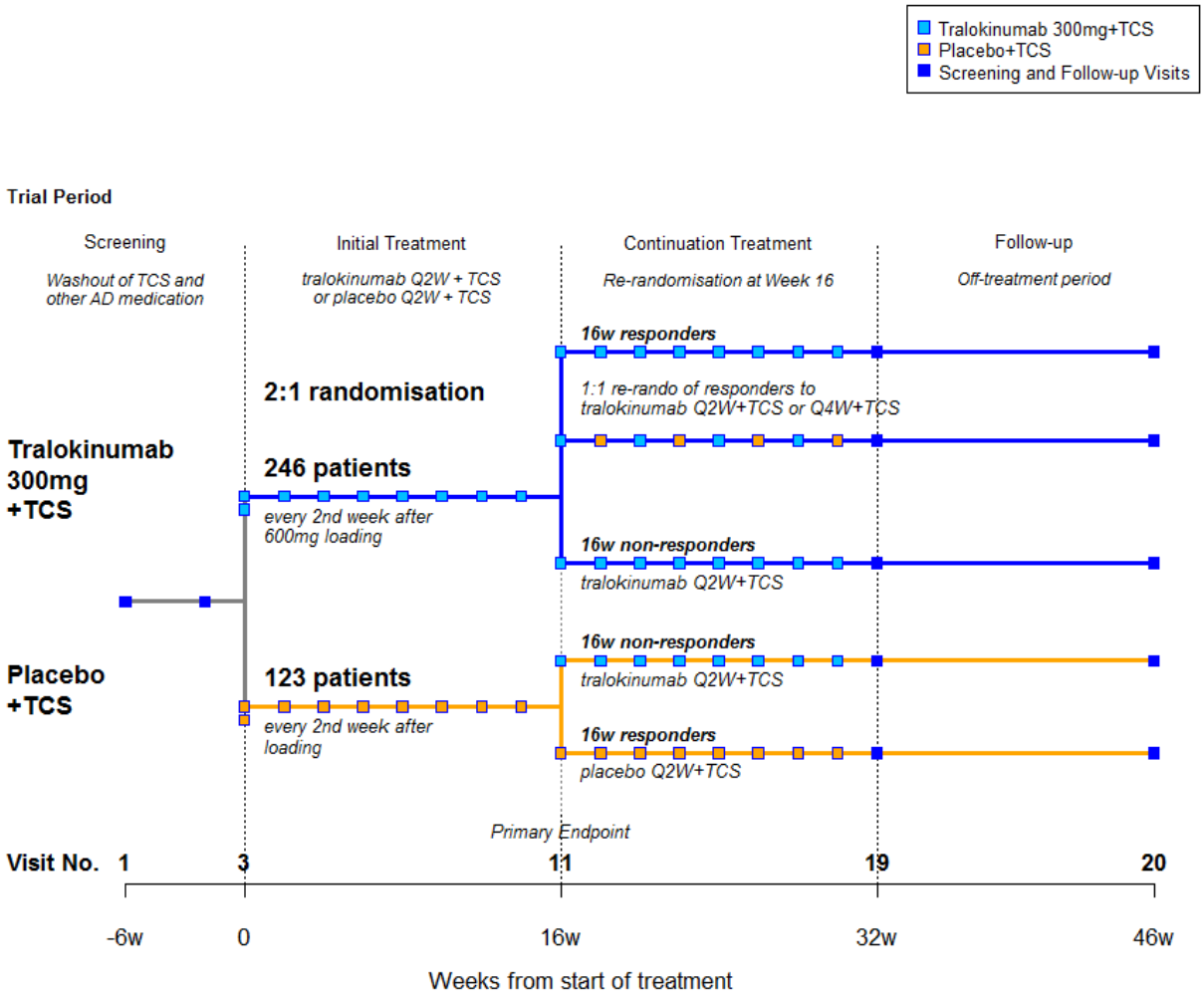
EudraCT number: 2017-002065-21

IND number: 123,797

ClinicalTrials.gov number: NCT03363854

3 Schematic of trial design

Panel 1 Trial design



Abbreviations: AD, atopic dermatitis; No, number; re-rando, re-randomisation; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids; w, week.
Note: Clinical response is defined as subjects achieving Investigator's Global Assessment response of 0 (clear) or 1 (almost clear) or at least 75% reduction in Eczema Area and Severity Index.

4 Schedule of procedures

Panel 2 Schedule of trial procedures: screening and treatment periods

	Screening		Treatment period																	Details (protocol section)
			Initial treatment									Continuation treatment								
Visit	**1**[1]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	
Visit window (days)[2]	**±3**	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Trial population and eligibility																				
Informed consent[3]	X																			8.4, Appendix 3B
Eligibility	X		X																	8.1 to 8.4
Trial products and randomisation																				
Randomisation			X								X[4]									9.2
Concomitant medication/procedures	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	9.4, 9.5
Initiation of emollients (background treatment)[5]		X																		9.3
IMP administration, compliance			X[6]	X[6]	X[6]	X	X	X	X	X	X[6]	X[6]	X[6]	X	X	X	X	X		9.1.1, 9.1.3.1, 9.2.1, 9.8.3, 9.8.3.1, 9.8.5
TCS (NIMP) dispensing			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		9.1.2, 9.1.3.2
TCS (NIMP) return				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	9.8.3.2, 9.8.5
Investigator assessments at baseline																				
C-SSRS	X																			10.2.1
Demographics (age), BSA	X		X																	10.2.2, 10.2.5
Other demographics and medical history	X																			10.2.2, 10.2.3
Height, weight			X																	10.2.4
Investigator assessment of efficacy																				
IGA, EASI	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	10.3.1.1, 10.3.1.2
SCORAD	X		X	X	X	X	X	X	X	X	X		X		X		X		X	10.3.1.3
Atopic dermatitis flares				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	10.3.1.4

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

	Screening		Treatment period																	Details (protocol section)
			Initial treatment									Continuation treatment								
Visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	
Visit window (days)[2]	**±3**	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Subject assessment of efficacy																				
eDiary training		X																		10.3.2
eDiary completion[7]		<- ========== ->																		
POEM			X	X	X	X	X		X		X		X				X		X	10.3.2.7
DLQI			X	X	X	X	X		X		X		X				X		X	10.3.2.8
EQ-5D-5L, HADS			X		X		X		X		X		X				X		X	10.3.2.9, 10.3.2.10
Safety assessments																				
Vital signs	X		X[6]	X[6]	X[6]	X	X	X	X	X	X[6]	X[6]	X[6]	X	X	X	X	X	X	10.4.1
Physical examination	X		X				X				X								X	10.4.2
ECGs	X		X				X				X				X				X	10.4.3
Serum pregnancy test, hepatitis B, C, HIV	X																			10.4.4, 10.4.5
Urine pregnancy test			X		X		X		X		X		X		X		X		X	10.4.4
Serum chemistry, haematology, IgE	X[8]		X		X		X		X		X		X		X		X		X	10.4.5
Urinalysis	X		X				X				X				X				X	10.4.5
Pharmacokinetics					X						X								X	10.4.6
Anti-drug antibodies			X		X						X								X	10.4.7
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	11, Appendix 1, Appendix 2

1) For subjects who do not require a wash-out and subjects who only require washout of topical AD treatment (as specified in the exclusion criteria in Section 8.3), visits 1 and 2 will be combined and screening will be reduced to 2 weeks. Hence, these subjects will only attend visit 2 (Week -2) which will include all assessments shown under Week -6. The screening period has a maximum duration of 6 weeks.

2) If the date of a subject visit does not conform to the trial plan, subsequent visits should be planned to maintain the visit schedule relative to randomisation/baseline.

3) The informed consent form must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations and washout of disallowed medications.
4) Re-randomisation at Week 16: the treatment during the continuation treatment period will depend on the regimen received in the initial treatment period and on the subject's clinical response at Week 16 (see Section 7.1). Subjects will continue their use of TCS.
5) All subjects must use an emollient twice daily (or more, as needed) for at least 14 days before randomisation and must continue this treatment throughout the trial (including safety follow-up).
6) For the first 3 IMP dosing visits (visits 3 to 5) and after re-randomisation (visits 11 to 13), subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 30 minutes with vital signs taken at 30 minutes or until stable, whichever is later (see Section 9.1.3.1).
7) eDiary includes: Eczema-related Sleep NRS, Worst Daily Pruritus NRS, Average Daily Pruritus NRS, Patient Days of Topical Treatment Use, PGI-B, and PGI-S; subjects will complete daily from Week -2 to 32, except for Patient Days of Topical Treatment Use which will be completed daily from Week 0 to 32.
8) IgE not assessed at screening.

Abbreviations: 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; NIMP, non-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; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid.

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

	SFU[1] (end of trial)	Nominal Week 16 visit[2] (if applicable)	Early termination[3] (if applicable)	Unscheduled visit[4] (if applicable)	Details (protocol section)
Visit	**20**	**11x**			
Week	**46**	**16**			
Visit window (days)	**±3**	**±3**			
Trial products					
Concomitant medication/procedures	X	X	X	X[4]	9.4, 9.5
IMP administration, compliance					
TCS (NIMP) dispensing				X[4]	9.1.2, 9.1.3.2
TCS (NIMP) return			X	X[4]	9.8.3.2, 9.8.5
Investigators global assessment of efficacy					
IGA, EASI		X	X	X[4]	10.3.1.1, 10.3.1.2
SCORAD		X	X	X[4]	10.3.1.3
Atopic dermatitis flares			X	X[4]	10.3.1.4
Subjects assessment of efficacy					
eDiary[5] completion		X	X	X[4]	10.3.2
POEM		X	X	X[4]	10.3.2.7
DLQI		X	X	X[4]	10.3.2.8
EQ-5D-5L, HADS			X	X[4]	10.3.2.9, 10.3.2.10
Safety assessments					
Vital signs	X		X	X[4]	10.4.1
Physical examination	X		X	X[4]	10.4.2
EGGs	X		X	X[4]	10.4.3
Urine pregnancy test	X		X	X[4]	10.4.4
Serum chemistry, haematology, IgE	X		X	X[4]	10.4.5
Urinalysis	X		X	X[4]	10.4.5
Pharmacokinetics	X		X	X[4]	10.4.6
Anti-drug antibodies	X		X	X[4]	10.4.7
Adverse events	X	X	X	X[4]	11, Appendix 1, Appendix 2

1) 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]) for whom the end of trial visit will be the last visit in the present trial before transfer to ECZTEND.
2) Subjects who permanently discontinue IMP prior to Week 16 will also attend the nominal Week 16 visit (visit 11x).
3) Assessments and procedures performed at Week 16 (see Panel 2) are also to be done at an early termination visit.
4) Assessments and procedures to be performed at an unscheduled visit are left at the investigator's discretion; except if due to atopic dermatitis flares, then as a minimum IGA, EASI, concomitant medications/procedures, and AEs are to be assessed.
5) eDiary includes: Eczema-related Sleep NRS, Worst Daily Pruritus NRS, Average Daily Pruritus NRS, Days of Topical Treatment Use, Patient Global Impression of Bother, and Patient Global Impression of Severity; subjects will complete daily (Week -2 to 32). Subjects who permanently discontinue IMP prior to Week 16 will complete the eDiary daily until the Nominal Week 16 visit.

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; eDiary, electronic diary; EQ-5D 5L, EuroQoL 5-Dimension Health Questionnaire 5 Level; HADS, Hospital Anxiety and

Depression Scale; IGA, Investigator's Global Assessment; IgE, immunoglobulin E; IMP, investigational medicinal product; NIMP, non-investigational medicinal product; NRS, numeric rating scale; POEM, Patient Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; SFU, safety follow-up; TCS, topical corticosteroid.

5 Introduction and 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).

AD is characterised by an activated T-helper-2 (Th2) pathway with increased skin expression of key Th2 cytokines including interleukin (IL)-13 (6, 7). The expression of IL-13 is increased in lesional skin compared to non-lesional skin, and the proportion of $CD4^+$ and $CD8^+$ cells expressing IL-13 is upregulated in AD patients compared to individuals without AD (6, 8).

IL-13 acts on keratinocytes to release C-C motif chemokine 22 (CCL22) and recruit more IL-13 expressing Th2 cells, decrease differentiation, and contribute to decreased barrier function (9). IL-13 also drives immunoglobulin E (IgE) production and contributes to mast cell activation status and, once allergen cross-links IgE on the cell surface, drives histamine release and induces itch (10, 11). Indeed, itch is a key issue in AD, which drives significant mechanical damage to the skin and further facilitates allergen and pathogen entry.

These effects together drive and exacerbate the disease phenotype. A review of the available preclinical literature from mouse and human *ex vivo* models suggests IL-13 as a, if not the, central mediator of the AD skin phenotype. Indeed, there is evidence that blocking the IL-4 receptor (which is part of the receptor complex which also binds IL-13) with the monoclonal antibody dupilumab leads to clinical improvement in subjects with AD (12).

5.2 Experience with investigational medicinal product

Tralokinumab is a human recombinant monoclonal antibody of the immunoglobulin G4 (IgG4) subclass that specifically binds to human IL-13 and blocks interaction with the IL-13 receptors (13-15). A compilation of clinical and nonclinical data on tralokinumab including pharmacokinetics (PK) is given in the current version of the Investigator's Brochure.

In total, 13 clinical trials with tralokinumab have been completed to date, with phase 3 development ongoing in AD and asthma. 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 version of the Investigator's Brochure.

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

In total, more than 2,296 subjects have been treated with tralokinumab (cut-off date: 18-Aug-2016). 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

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

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

Since TCS represent the mainstay of pharmacological treatment of AD, many patients may use tralokinumab in combination with TCS and this trial is intended to inform about treatment and maintenance with concomitant use of tralokinumab and TCS. After a 16-week initial treatment period, the trial will evaluate 2 different treatment options for additional 16-weeks of maintenance therapy in the continuation treatment period (tralokinumab 300 mg Q2W and 300 mg every 4 weeks [Q4W]).

The primary objective of this trial is to demonstrate that tralokinumab in combination with TCS provides more effective control of the skin manifestations of AD than placebo in combination with TCS. 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 (HRQoL) measures related to AD.

Thus, the trial will further contribute to the characterisation of the benefit-risk profile of tralokinumab.

5.4 Justification for dose

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

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

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

In the continuation treatment period, one 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 evaluate whether less frequent dosing of tralokinumab in combination with TCS therapy may be sufficient for 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. Albeit dupilumab exhibits an acceptable benefit-risk ratio in clinical trials in AD, the long-term efficacy and safety experience with dupilumab is currently limited.

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 individuals with AD may benefit from treatment with tralokinumab.

In the clinical trials completed to date, tralokinumab was well tolerated. A number of theoretical potential risks have been identified that are described in the current version of the Investigator's Brochure, including hypersensitivity reactions, immune complex disease, severe infections, malignancies, and interference with reproductive function; measures are in place in this trial to protect participating subjects as follows:

- Close monitoring of subjects during the trial with trial visits every 2 weeks during the treatment period (see the schedule of procedures in Section 4).
- Close monitoring of subjects during the post-dosing period at the first 3 investigational medicinal product (IMP) dosing visits in the initial treatment period (i.e., Weeks 0, 2, and 4) and after re-randomisation (i.e., Weeks 16, 18, and 20) as a precautionary measure against hypersensitivity reactions (further details are given in Section 9.1.3.1).

- Monitoring of subjects for clinical manifestations that may be associated with the development of specific antibodies to tralokinumab (i.e., immune complex disease).
- Exclusion of subjects with untreated systemic helminth infestations or subjects who have failed to respond to standard of care therapy; neutralisation of IL-13 might theoretically cause a worsening of parasitic infestation, in particular prevention of expulsion of gastrointestinal worms (helminths) (19).
- 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 potential 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 in combination with TCS therapy 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 must agree to use a highly effective method of contraception to prevent pregnancy during the clinical trial and until 16 weeks after discontinuation of treatment with the IMP. In addition, all female subjects of child-bearing potential will have a pregnancy test performed before, during and at end-of-treatment to ensure that no foetuses are exposed to the IMP.

In a 13-week repeated-dose nonclinical study in male cynomolgus monkeys, no adverse effects on male reproductive endpoints were observed (Investigator's Brochure). Coupled with the negligible exposure risk for drugs and antibodies by way of semen to achieve meaningful pharmacological levels in a pregnant woman or in the conceptus (20), it is not

considered necessary to impose restrictions on fathering a child or sperm donation in clinical trials with tralokinumab.

In this trial in adult subjects with moderate-to-severe AD who are otherwise healthy, the efficacy of tralokinumab in combination with TCS therapy will be compared with a placebo control group on TCS therapy. The choice of placebo (on the background of TCS) as control is appropriate for addressing the objectives of this trial and it will provide information regarding treatment with tralokinumab in combination with TCS. Subjects will be under supervision by a dermatologist or allergist every second week for the duration of the treatment period, which is more frequent than standard clinical practice. All subjects will be treated with TCS (Europe: Class 3 [potent]; US: Class 4 [mid-strength]) as needed, and rescue treatment may be given to the subjects at the investigator's discretion for the duration of the trial. Moreover, 67% of the subjects will be randomised to treatment with tralokinumab in the initial treatment period, and except for those with a clinical response in the placebo group at Week 16, all subjects will be treated with tralokinumab in the continuation period with a potential effect and benefit for the individual subject. This will ensure that the subject's AD is carefully monitored and treated as needed in this trial. If subjects are rescued with systemic corticosteroids or nonsteroid immunosuppressants they must discontinue IMP but may be eligible to restart IMP after discontinuing such rescue treatment.

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.

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

In conclusion, the trial design chosen for this efficacy and safety trial on tralokinumab in combination with TCS therapy 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 continuation treatment period (Week 16 until Week 32). All objectives and corresponding endpoints are listed in Panel 4.

Panel 4 Objectives and endpoints

Objectives	Endpoints
Primary objective	Primary endpoints
To demonstrate that tralokinumab in combination with TCS is superior to placebo in combination with TCS in treating moderate-to-severe AD.	• IGA score of 0 (clear) or 1 (almost clear) at Week 16. • EASI75 at Week 16.
Secondary objective	Secondary endpoints
To evaluate the efficacy of tralokinumab in combination with TCS on severity and extent of AD, itch, and health related quality of life compared with placebo in combination with TCS.	*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. *Health-related quality of life* • Change in DLQI score from baseline to Week 16.
Additional secondary objectives	Additional secondary endpoints
To assess the safety of tralokinumab in combination with TCS when used to treat moderate-to-severe AD for 32 weeks.	• AE/SAE frequency by preferred term. • Frequency of anti-drug antibodies.
To evaluate the efficacy of tralokinumab in combination with TCS on health care resource utilisation compared with placebo in combination with TCS.	• Amount of TCS used through Week 16 (assessed as the amount of TCS weighted from previous visits). • Number of AD flares through Week 16. • Number of days without topical treatment use from baseline to Week 16 (according to Patient Days of Topical Treatment Use).
To support the primary and secondary objectives in the trial.	*Supporting primary endpoints* • EASI50 at Week 16. • EASI90 at Week 16. • Change from baseline to Week 16 in EASI score. *Supporting severity and extent of AD* • SCORAD75 at Week 16. • SCORAD50 at Week 16.

Panel 4 Objectives and endpoints (continued)

Objectives	Endpoints
Additional secondary objectives	Additional secondary endpoints
To support the primary and secondary objectives in the trial (continued).	*Supporting itch* • Change from baseline to Week 16 in Worst Daily Pruritus NRS (weekly average). *Supporting health-related quality of life* • Reduction from baseline to Week 16 of DLQI of ≥4 points among subjects with baseline DLQI ≥4.
Maintenance objective	Maintenance endpoints
To evaluate the maintenance of effect of tralokinumab in combination with TCS when used to treat moderate to severe AD for 32 weeks for subjects achieving clinical response at Week 16.	• IGA of 0/1 at Week 32 among subjects with IGA of 0/1 at Week 16 after initial randomisation to tralokinumab. • EASI75 at Week 32 among subjects with EASI75 at Week 16 after initial randomisation to tralokinumab.
Other objectives	Other endpoints
To evaluate the efficacy over time of tralokinumab in combination with TCS on severity and extent of AD, itch, and health related quality of life compared with placebo in combination with TCS.	• 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 scheduled assessment through Week 4 to 14 in Worst Daily Pruritus NRS (weekly average). • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to each scheduled assessment through Week 4 to 14. • Change in DLQI score from baseline to each scheduled assessment until Week 14.

To evaluate the efficacy of tralokinumab in combination with TCS on patient-reported outcomes compared with placebo in combination with TCS.	• Change in Eczema-related Sleep NRS (weekly average) from baseline to Week 16. • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to Week 2. • Change in Worst Daily Pruritus NRS (weekly average) from baseline to Week 2. • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 3 from baseline to Week 16. • Reduction of Worst Daily Pruritus NRS (weekly average) of at least 3 from baseline to Week 2. • Change in POEM score from baseline to Week 16. • Reduction from baseline to Week 16 of POEM score ≥4 points in subjects with baseline POEM score ≥4. • Change in EQ-5D-5L from baseline to Week 16. • Change in HADS from baseline to Week 16. • HADS anxiety and HADS depression subscale scores <8 at Week 16 in subjects with baseline HADS anxiety or HADS depression subscale scores ≥8.

Abbreviations: 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; TCS, topical corticosteroid.

7 Trial design

7.1 Overall trial design

Overview

This is a randomised, double-blinded, placebo-controlled phase 3 trial to confirm the efficacy and safety of tralokinumab administered on a background of TCS therapy 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 continuation treatment period of 16 weeks (Weeks 16 to 32). The primary endpoints are assessed at Week 16, and the final efficacy assessment will be performed at Week 32. An off-treatment follow-up period for the assessment of safety is also included (Weeks 32 to 46). A schematic of the trial design is provided in Panel 1.

Screening period (Week -6 to Week 0)

The screening period has a minimum duration of 2 weeks and a maximum duration of 6 weeks and includes 1 or 2 screening visits. The exact duration of the screening period for

the individual subject depends on the length of any washout period needed, as specified in the exclusion criteria in Section 8.3 (i.e. 4 weeks prior to randomisation for systemic immunosuppressive/immunomodulating drugs, systemic corticosteroid use, or three or more bleach baths during any week within the 4 weeks; 2 weeks prior to randomisation for TCSs, TCIs, or topical phosphodiesterase 4 [PDE-4] inhibitors). If no washout or a 2-week washout period is required, screening will be reduced to 2 weeks and reduced to 1 visit (Week -2; visit 2), i.e., the 2 screening visits will be merged. Eligibility will be assessed at the (first) screening visit and on Day 0 (hereinafter "baseline") prior to randomisation.

All subjects will attend a screening visit 14 days before baseline (Week -2; visit 2) where they will receive electronic diary (eDiary) training and start the eDiary. Data entered into the eDiary during the 2 weeks before randomisation (including the data collected on the day of the baseline visit [visit 3]) will be used to calculate baseline values of the patient-reported outcomes (PROs).

All subjects will use an emollient twice daily (or more, as needed) for at least 14 days before randomisation and will continue this treatment throughout the trial (including safety follow-up). Subjects will initiate emollient treatment no later than the Week -2 visit. On lesional skin, emollients should only be applied at times where TCS is not applied (i.e., emollients and TCS should not be used on the same areas at the same time of day); on TCS-untreated areas, the emollients may be applied at all times.

Initial treatment period (Week 0 to Week 16)

Following the screening period, approximately 369 subjects will be randomised 2:1 to one of the following groups stratified by region (Europe and North America) and baseline disease severity (IGA 3 or 4):

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

Doses will be administered at the trial site by subcutaneous (SC) injection.

Subjects in both treatment groups will apply a thin film of a supplied TCS (Europe: Class 3 [potent]; US: Class 4 [mid-strength]) once daily to areas with active lesions as needed; lower potency TCS or TCI may be prescribed if needed on body areas where the supplied TCS is not advisable or on areas where continued treatment with TCS is considered unsafe. Topical therapy will be discontinued when control is achieved; discontinuation should preferably be

gradual. The safety and appropriateness of continued or repeated courses of TCS therapy will be monitored and supervised by site staff.

Continuation treatment period (Week 16 to Week 32)

At Week 16, all subjects will be assigned to continuation treatment that will carry on until Week 32 (the last dose of IMP will be administered at Week 30). The treatment during the continuation period will depend on the regimen received in the initial treatment period and on the subject's clinical response at Week 16. Clinical response is defined as IGA of 0 or 1 or EASI75.

Subjects randomised to tralokinumab in the initial treatment period and with a clinical response at Week 16 will be re-randomised 1:1 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 of tralokinumab 300 mg (2 mL) and placebo (2 mL) ('tralokinumab Q4W').

Subjects randomised to placebo in the initial treatment period and with a clinical response at Week 16 will continue to receive placebo Q2W in the continuation treatment period.

Subjects randomised to tralokinumab or placebo in the initial treatment period who do not fulfil either of the criteria for clinical response at Week 16 will receive tralokinumab Q2W in the continuation treatment period.

All subjects will stay on the TCS regimen during the continuation treatment period.

Safety follow-up period (Week 32 to Week 46)

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

Long-term extension trial (selected countries)

Eligible subjects may be invited to enter a long-term extension trial conducted under a separate protocol (LP0162-1337, ECZTEND). Subjects who transfer to ECZTEND must have had their last visit in the treatment period (Week 32 under the current protocol).

7.2 Number of subjects needed

Assuming a screening failure rate of 25%, approximately 492 subjects will be screened and approximately 369 subjects will be randomly assigned to the initial treatment period (2:1; 246 subjects in the tralokinumab group and 123 subjects in the placebo group). At Week 16, approximately 40% of the tralokinumab treated subjects are expected to be re-randomised (1:1 to tralokinumab Q2W or tralokinumab Q4W) into the continuation treatment period. Randomisation and re-randomisation will be handled in the interactive web response system (IWRS) to ensure continued blinding in the trial (see Section 9.2.1).

The statistical power considerations for this sample size (n=369) are described in Section 12.1.

This trial will be conducted at approximately 70 sites in Europe and North America. 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 (Week 46). Subjects entering the long-term extension trial (LP0162-1337, ECZTEND) after completion of the end of treatment visit (Week 32) 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.

7.4 Scientific rationale for trial design

The trial is designed to evaluate the efficacy and safety of tralokinumab in combination with TCS therapy versus placebo with TCS in subjects with moderate-to-severe AD. The trial endpoints have been selected to evaluate the efficacy of tralokinumab in improving the severity and extent of AD including both objective signs of disease and subjective symptoms (e.g. itch) as well as HRQoL. The two primary efficacy endpoints IGA score of 0 or 1 and EASI75 are recognised as important endpoints in clinical trials in AD by regulators in the US and EU, respectively.

The planned trial design is considered appropriate for evaluating the trial objectives, as the double-blind conditions regarding the subject's treatment (tralokinumab or placebo) are maintained and the possible observer bias regarding treatment effects are minimised.

Stratification by region (Europe and North America) and baseline disease severity (IGA 3 or 4) in this multi-centre trial will provide a strong basis for generalisation of the findings to the target patient population. Further, the trial population will comprise male and female subjects to explore effects between genders and across the adult age range.

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

The most important inclusion criterion for entry into the trial is an established diagnosis of AD (as defined by the Hanifin and Rajka 1980 criteria for AD)(21) at screening and a history of AD for at least one year, to ensure correct diagnosis and rule out differential diagnosis. A prerequisite for inclusion into the trial is a documented history of topical AD treatment failure (due to inadequate response), to ensure that the subject is candidate for systemic treatment. Subjects for whom topical treatment with TCS are medically inadvisable may not be enrolled as TCS therapy will be administered in this trial.

AD is a chronic condition and the 32-week treatment duration has been chosen to evaluate the maintenance of effect as well as the safety and tolerability of tralokinumab in combination with TCS therapy. Data on antibodies against tralokinumab (i.e., ADAs) and tralokinumab drug concentration (i.e., PK) will be collected and the assessment of the potential for immunogenicity in the context of continuous treatment will also be evaluated up until 16 weeks after last dose of trial product to ensure adequate washout (approximately 5 times the half-life) of tralokinumab.

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 Section 4.

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 (21; Appendix 4).

4. History of AD for ≥1 year.

5. Subjects who have a recent history (within 1 year before the screening visit) of inadequate response to treatment with topical medications.

    - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to higher potency (±TCI as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent TCS), whichever is shorter.
    - Subjects with documented systemic treatment for AD in the past year are also considered as inadequate responders to topical treatments and are potentially eligible for treatment with tralokinumab after appropriate washout.

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

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

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

9. A Worst Daily Pruritus 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.

11. Women of child-bearing potential must use a highly effective* form of birth control (confirmed by the investigator) throughout the trial and at least for 16 weeks (5 half-lives) after last administration of IMP.

    *A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year) such as bilateral tubal occlusion, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), sexual abstinence (when this is in line with the preferred and usual life style of the subject), vasectomised partner (given that the subject is monogamous). The subjects must have used the contraceptive method continuously for at least 1 month prior to the pregnancy test at baseline. A female is defined as not being of child-bearing potential if she is postmenopausal (at least 12 months with no menses without an alternative medical cause prior to screening), or surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy).

8.3 Exclusion criteria

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

2. Concurrent enrolment in another clinical trial where the subject is receiving an IMP.
3. Previous randomisation in a tralokinumab clinical trial.
4. Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis.
5. Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD.
6. Use of tanning beds or phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]), within 6 weeks prior to randomisation.
7. Treatment with the following medications within 4 weeks prior to randomisation:
    - Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine, azathioprine, mycophenolate-mofetil, Janus kinase inhibitors).
    - Systemic corticosteroid use (excludes topical, inhaled, or intranasal delivery).
    - Three or more bleach baths during any week within the 4 weeks.
8. Treatment with the following medications within 2 weeks prior to randomisation
    - TCS.
    - TCI.
    - Topical phosphodiesterase 4 (PDE-4) inhibitor.
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) is allowed, provided they are not administered within 5 days before/after any trial visit.
10. Receipt of any marketed biological therapy (i.e. immunoglobulin, anti-IgE) including dupilumab or investigational biologic agents:
    - Any cell-depleting agents including but not limited to rituximab: within 6 months prior to randomisation, or until lymphocyte count returns to normal, whichever is longer.
    - Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to randomisation.

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

22. History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at screening, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.
23. History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
24. History of attempted suicide or 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 Enrolment

Trial participation begins once written informed consent is obtained (see Appendix 3B for details on the informed consent process). Once informed consent is obtained, a subject identification number (subject ID) will be assigned by a central 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 (22) and to respond to queries from regulatory authorities. Minimal information includes demography, screening failure details, eligibility criteria, and reporting of any 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 informed consent, 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.

8.5 Discontinuation

A subject may withdraw from trial or from treatment at any time (prior to first dose or during the 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 9.7.1.

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 schedule of procedures [Panel 3] 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 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

9.1.1 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. It is presented as a liquid formulation for SC administration.

Tralokinumab and placebo will be packaged in individually numbered kits, each containing 1 pre-filled syringe. Refer to Panel 5 for further details.

Panel 5 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 50 mM sodium acetate/acetic acid buffer, 85 mM 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 pre-filled syringe is a single-use, disposable system that is designed to administer the labelled dose of the system to the subcutaneous space during 1 injection and automatically provide a safety mechanism to reduce the occurrence of accidental needle sticks during disposal of the system.

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

9.1.2 Non-investigational medicinal product

Each subject will be prescribed a non-investigational medicinal product (NIMP) for the duration of the trial: the subjects will receive a TCS cream (Europe: Class 3 [potent]; US: Class 4 [mid-strength]) from randomisation (Week 0) to Week 32. This will be provided as mometasone furoate, 0.1% cream in kit sizes of 180–225 g every 2 weeks. This should be the only TCS product applied to the body during this period, excluding areas of the body where the supplied TCS is not advisable or where continued use is considered unsafe (see Section 9.1.3.2 for further details).

9.1.3 Administration of trial products

9.1.3.1 Administration of IMP

The IWRS will assign the required IMP 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.

At subsequent visits 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 (Q2W).

Subjects in the continuation treatment period will receive either:

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

Dosing visits are shown in the schedule of procedures (Section 4). The last administration of IMP will occur at Week 30.

IMP will be administered by a qualified, unblinded healthcare professional (HCP; see Section 9.2.1 for blinding details). 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 a drug handling manual.
IMP administration must be carried out according to these instructions.

After IMP administration

For the first 3 IMP dosing visits in both the initial treatment period (i.e., Weeks 0, 2, and 4) and after re-randomisation (i.e. Weeks 16, 18, and 20), subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 30 minutes with vital signs taken at 30 minutes or until stable, whichever is later. Vital signs will be documented in the eCRF.

As with any antibody, allergic reactions to dose administration are possible. The World Allergy Organization has categorised anaphylaxis into 2 subgroups: allergic anaphylaxis (mediated by an immunologic mechanism) and nonallergic anaphylaxis (which has a nonimmunologic cause) (23). The clinical criteria for defining anaphylaxis for this trial are listed in Appendix 5 (24). Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc., and medical equipment to treat acute anaphylactic reactions must be immediately available at the trial sites, and trial personnel should be trained to recognise and respond to anaphylaxis according to local guidelines.

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

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) within 72 hours prior to IMP administration.

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

9.1.3.2 Administration of NIMP

The IWRS will assign the required NIMP (TCS) kit numbers for each subject at each dispensing visit. The NIMP will be provided as mometasone furoate, 0.1% cream in kit sizes of 180–225 g every 2 weeks. If needed, additional NIMP kit(s) may be dispensed to the subject at a scheduled or unscheduled visit at the investigator's discretion. The amount of additional NIMP dispensed must be recorded in the eCRF.

Subjects will be instructed to apply a thin film of the dispensed TCS (Europe: Class 3 [potent]; US: Class 4 [mid-strength]) once daily to active lesions, as needed. The TCS should be discontinued when control is achieved; discontinuation should preferably be gradual and the maximum duration of treatment should not exceed 3 weeks. The safety and appropriateness of continued or repeated courses of TCS therapy will be monitored and supervised by site staff.

From randomisation (Week 0) through Week 30, the TCS will be dispensed and the subject must return used and unused TCS tubes at each subsequent trial visit, to assess the amount of medication used. The subjects must be instructed by the site staff on the importance of returning all used and unused TCS tubes. The site staff will return used and unused TCS tubes to the contract manufacturing organisation (CMO). The TCS tubes will be weighed at the CMO before shipment to the trial sites and again upon return.

An additional, lower potency TCS or TCI may be used at the investigator's discretion on areas of the body where use of the supplied TCS is not advisable such as areas of thin skin (face, skin fold areas, genital areas, etc.) or on areas where continued treatment is considered unsafe. The low potency TCS and TCI will not be provided by LEO and will not be weighed, but must be registered in the eCRF as concomitant medications (see Section 9.4).

Further details on NIMP dispensing are provided in a drug handling manual.
NIMP administration must be carried out according to these instructions.

9.2 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. Treatment assignment will be pre-planned according to a computer-generated randomisation schedule in a 2:1 ratio (tralokinumab:placebo) stratified by region (Europe and North America) and baseline disease severity (IGA of 3 or 4).

Subjects will be re-randomised to continuation treatment at Week 16. The treatment during this period will depend on the regimen received in the initial treatment period and the subject's clinical response at Week 16. Subjects randomised to tralokinumab who have a clinical response at Week 16 (i.e. IGA 0/1 or EASI75), will be re-randomised to the continuation treatment period in a 1:1 ratio (tralokinumab Q2W:tralokinumab Q4W) stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1). Subjects randomised to placebo who have a clinical response at Week 16 will continue on placebo. Subjects in either the tralokinumab or placebo group who have not achieved a clinical response at Week 16 will receive tralokinumab Q2W in the continuation treatment period.

IWRS will be used to control randomisation, re-randomisation, and stratification factors, along with IMP supply chain and expiry tracking, and for dispensing and return of NIMP (TCS).

9.2.1 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. IMP is packed in identical boxes, with non-sequential kit numbers to ensure that unblinding does not occur during shipment and handling of the drug.

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

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

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

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.

To support submission for marketing approval, an analysis of trial data up to and including visit 19 (Week 32) will be performed and will require unblinding of data. To perform this analysis, an Analysis Group consisting of a Medical Expert, a Statistician, a Statistical Programmer and a Medical Writer will be unblinded to individual subject treatment allocation following database lock for the 32-week data. All staff involved in the conduct of the trial will remain blinded to treatment allocation for the entire duration of the trial. This principle will be applied to all investigator staff and to staff employed by the sponsor except for those who are directly involved in the execution of the analysis. See Section 12.3.11 for details regarding the statistical aspects of the analysis of data up to Week 32.

9.2.2 Emergency unblinding of individual subject treatment

While the safety of a subject always comes first, it is still important to carefully consider if unblinding is necessary to ensure a subject's safety. An emergency unblinding request can be made by the investigators, other HCPs who are not members of the trial staff, or authorised LEO 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 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 3B) to be used if the investigator or delegated site staff cannot be reached. The requester will provide the trial ID and subject ID to the emergency unblinding CRO who will immediately reveal the individual treatment allocation.

The emergency unblinding CRO will clarify that the requester requires immediate unblinding without further medical consultation. Should the requester wish to discuss whether unblinding is necessary, the emergency unblinding CRO will provide the requester with the LEO 24/7 contact which will be diverted to the medical cover.

9.3 Background treatment (emollients)

All subjects must use an emollient twice daily (or more, as needed) for at least 14 days before randomisation; the background treatment should preferably be an additive free, basic bland emollient. On lesional skin, emollients should only be applied at times where TCS is not

applied (i.e., emollients and TCS should not be used on the same areas at the same time of day); on TCS-untreated areas, the emollients may be applied at all times. Subjects must continue their background emollient treatment throughout the trial (including safety follow-up).

9.4 Concomitant medication and procedures

Any medication or vaccine that the subject receives from 3 months prior to screening through safety follow-up (Week 46) 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.

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 9.5. 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.

All subjects will receive a TCS (Europe: Class 3 [potent]; US: Class 4 [mid-strength]) for treatment of their AD from randomisation through the treatment periods (Week 0 to 32) to be used as needed based on the subject's own judgement (see Section 9.1.3.2 for details regarding dispensing of TCS [NIMP]). Low potency TCS or TCI may be used at the investigator's discretion on areas of the body where use of the supplied TCS is medically inadvisable such as areas of thin skin (face, skin fold areas, genital areas, etc.) or on areas where continued treatment is considered unsafe. Low potency TCS or TCI must be reported as concomitant medications.

In addition, the following concomitant medications related to AD treatment are permitted from screening through safety follow-up (Week 46):

- Oral antibiotics, antiviral, or antifungal therapy for skin infections as appropriate.
- Stable doses of an emollient (see Section 9.3; 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.

9.5 Prohibited medication and procedures

The following medications are prohibited during the trial from randomisation (Week 0) through Week 32:

- Use of ultraviolet A or B (UVA or UVB), psoralen + UVA (PUVA), other phototherapy, or tanning beds.
- 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 (Week 0 to 46):

- Other topical medications used for the treatment of AD other than the supplied TCS, except lower potency TCS or TCI which may be used at the investigator's discretion on areas of the body where use of the supplied TCS is not advisable.
- 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, dupilumab 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.

9.6 Rescue treatment

If medically necessary (i.e., to control intolerable AD symptoms), rescue treatment for AD may be provided to trial subjects at the discretion of the investigator. If possible, investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for subjects who do not respond adequately after at least 14 days of topical treatment. The subject will be monitored for signs of local or systemic TCS toxicity and the safety and appropriateness of continued use will be supervised by site staff. For reporting of AD flares see Section 10.3.1.4.

Subjects who receive topical rescue treatment (higher potency TCS: Europe Class >3; US Class <4) will continue IMP 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 9.7.2, 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 (at least disease severity scores [IGA and EASI], concomitant medications/procedures, and AEs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose, if necessary.

In the primary efficacy analyses, subjects who receive topical or systemic rescue treatment during the treatment periods will be considered as non-responders.

9.7 Dose modification and IMP discontinuation rules

9.7.1 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 >3×ULN with total bilirubin >2×ULN (unless elevated bilirubin is related to Gilbert-Meulengracht Syndrome).
    - Confirmed AST and/or ALT >5×ULN (for more than 2 weeks).

Subjects who in the opinion of the subject or investigator have unacceptable treatment effect of IMP in combination with TCS therapy may discontinue treatment permanently and enter the safety follow-up period.

Refer to Section 8.5 for details on the handling of subject discontinuation and Panel 3 for assessments to be performed at an early termination visit for subjects who discontinue IMP permanently.

9.7.2 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, dupilumab or other biologics). IMP dosing may be resumed after the medication leading to suspension of IMP is discontinued; see Section 9.6 for details regarding re-initiation of IMP after discontinuation of systemic rescue treatment.

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.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

9.8.1.1 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.

9.8.1.2 Labelling and packaging of NIMP

The NIMP (TCS) will be packaged in individually numbered kits that contain tubes of TCS cream with a total weight of 180–225 g.

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

The labelling of NIMPs 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.

9.8.2 Storage of trial products

9.8.2.1 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 instructions for further details) and reported as a product complaint to Global Pharmacovigilance, LEO (see Section 9.10). Damaged IMP should not be used.

9.8.2.2 Storage of NIMP

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

The NIMP must be stored at room temperature at the site according to the approved local label for mometasone furoate. 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 NIMP 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 NIMP 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 NIMP should be documented via IWRS (refer to the IWRS instructions for further details) and reported as a product complaint to Global Pharmacovigilance, LEO (see Section 9.10). Damaged NIMP should not be used.

9.8.3 Drug accountability

9.8.3.1 IMP accountability

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

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 CMO.

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

9.8.3.2 NIMP accountability

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

An inventory (trial medication inventory log) must be kept of the NIMP 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 NIMP.

Full drug accountability will also be performed in the IWRS. Furthermore, the number of TCS tubes returned by the subject must be documented in the eCRF by the trial staff.

The trial site will maintain trial kit cartons from used kits until reconciliation. The NIMP will be fully accounted for by the CRA. Accountability will 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 used and unused NIMP tubes supplied by the CMO on behalf of LEO will be returned to the CMO. NIMP may be returned from the trial site either to the CMO directly or via the LEO affiliate or CRO responsible for the running of the clinical trial. All returned NIMP tubes will be weighed by the CMO to determine the amount of TCS used by the subject and will be reconciled with the individual drug accountability forms. The detailed procedure for weighing of NIMP tubes and subsequent transfer of tube weight data to the clinical database will be documented.

9.8.4 Trial product destruction

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

9.8.5 Treatment compliance

IMP injections will be performed by site staff that will also hand-out NIMP (TCS) for self-administration and keep the accountability records up to date.

Any non-compliance with IMP administration and dispensing and return of NIMP and the reason for it must be recorded in the eCRF.

9.9 Provision for subject care following trial completion

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

9.10 Reporting product complaints

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

knowledge. Critical product complaints must be reported to Global Pharmacovigilance at LEO within 24 hours. Critical product complaints are defined as issues, defects, or device deficiencies that has or potentially could have a serious impact for the subject (e.g., SAE, or large particles in the syringe).

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 IMP device deficiency will be reported by the investigator as described in Sections 11.2 and 11.3. Similarly, any defects or issues with the NIMP (TCS) must also be reported to Global Pharmacovigilance at LEO using the same complaint procedure as for the IMP and IMP device.

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

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

Product complaints will be reported to Global Pharmacovigilance at LEO using the fax number or email address below:

Fax number: +45 7226 3287

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

10Trial schedule and assessments

10.1 Overview

During the trial, there are 20 scheduled site visits at the clinic. The visits and procedures to be carried out at each visit, as well as the intervals between visits, are summarised as trial flow charts in the schedule of procedures (Section 4). Refer to Panel 2 for assessments during screening and treatment, to Panel 3 for assessments during follow-up (including early termination, nominal Week 16 visit [for subjects who permanently discontinue IMP prior to Week 16] and unscheduled visits), and to Section 7 for further details on the trial design.

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 preferably 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.
    4. AD flares
- Safety and laboratory assessments.
- Administration of IMP.
- Dispensing of NIMP (TCS).

Subjects may also need to be seen at unscheduled visits during the course of the trial. The assessments to be performed at an unscheduled visit are left at the investigator's discretion (could include any assessment performed at an early termination visit) (Panel 3), except if the reason is an AD flare in which case IGA, EASI, concomitant medications/procedures, and AEs should be collected (see Section 10.3.1.4).

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 (see Section 9.2.1).

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 (see 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 the lifetime history and severity of suicidal ideation and suicidal behaviour through a series of simple, plain-language questions (25). The C-SSRS must be completed at screening to check that exclusion criterion no. 24 does not apply. Further details on the assessment according to the C-SSRS are included in the efficacy assessment & C-SSRS manual.

10.2.2 Demographics

The following demographic data will be recorded:

- Age: Month and/or 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 as component A of SCORAD (see Section 10.3.1.3) and will be reported as a percentage of all major body sections combined. The following body regions will be assessed (brackets show the highest possible score for each region): head and neck (9%), anterior trunk (18%), back (18%), upper limbs (18%), lower limbs (36%), and genitals (1%). The total BSA score will be assessed according to the schedule of procedures (Section 4).

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 6). The IGA score will be assessed according to the schedule of procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. Whenever possible, the IGA should be assessed by the same investigator at each visit to reduce inter-rater variability. The IGA is included in the efficacy assessment & C-SSRS manual.

Panel 6 Investigator's Global Assessment

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

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 (26). Details on the scoring of severity and extent of AD according to EASI are included in the efficacy assessment & C-SSRS manual.

The EASI score will be assessed according to the schedule of procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. Whenever possible, the EASI 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 7. Briefly, the investigator will assess the severity of 4 AD disease characteristics (erythema, induration/papulation, excoriation, and lichenification) on the 4 body regions (head/neck, trunk, upper extremities, lower extremities); severity will be assessed according to the scale shown in Panel 8. For each body region, a severity sum score will be calculated which will be multiplied by an area score (Panel 8) and by a weighting factor. The EASI score equals the sum of the scores obtained for each body region (Panel 7).

Panel 7 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)	× AS	× 0.1	
Trunk	(SS +	SS +	SS +	SS)	× AS	× 0.3	
Upper extremities	(SS +	SS +	SS +	SS)	× AS	× 0.2	
Lower extremities	(SS +	SS +	SS +	SS)	× AS	× 0.4	
The EASI score is the sum of the 4 body region scores							_____ (range 0-72)

Abbreviations: AS, area score; EASI, Eczema Area and Severity Index; SS, severity score.
Modified from (27).

Panel 8 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

Abbreviations: 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 (28). Details on the scoring of extent and severity of AD according to SCORAD are included in the efficacy assessment & C-SSRS manual. The maximum total score is 103, with higher values indicating more severe disease. SCORAD will be assessed according to the schedule of procedures (Section 4).

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

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

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

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

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

Note: dryness is evaluated on uninvolved areas.

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

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

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

10.3.1.4 Atopic dermatitis flares

An AD flare is defined as an acute, clinically significant worsening of signs and symptoms of AD requiring therapeutic intervention (29). For the purpose of this protocol, AD flares are defined as worsening of the disease that requires escalation/intensification of AD treatment reported after initiation of IMP; this will also include initiation or intensification of the TCS (NIMP) supplied to the subjects. Flares will be assessed at the clinic according to the schedule of procedures (see Section 4). Subjects who experience disease worsening between scheduled trial visits should return to the clinic for an unscheduled visit for assessment of flare before initiating the treatment escalation; subjects who return to the clinic for assessment of flares at an unscheduled visit should undergo IGA and EASI assessments, and information on concomitant medications/procedures and AEs should be collected.

Details on rescue treatments and prohibited concomitant medications and procedures for treatment of AD are provided in Sections 9.6 and 9.5.

10.3.2 Subject assessments

Six PROs will be assessed daily using an eDiary:

- Eczema-related Sleep NRS (Section 10.3.2.1).
- Worst Daily Pruritus NRS (Section 10.3.2.2).
- Average Daily Pruritus NRS (Section 10.3.2.3).
- Patient Days of Topical Treatment Use (Section 10.3.2.4).
- Patient Global Impression of Bother (PGI-B) (Section 10.3.2.5.
- Patient Global Impression of Severity (PGI-S) (Section 10.3.2.6).

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

In addition, 4 PROs will be completed by the subjects at the site:

- Patient Oriented Eczema Measure (POEM) (Section 10.3.2.7).
- Dermatology Life Quality Index (DLQI) (Section 10.3.2.8).
- EuroQoL 5-Dimension Health Questionnaire 5 Level (EQ-5D-5L) (Section 10.3.2.9).

- Hospital Anxiety and Depression Scale (HADS) (Section 10.3.2.10).

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 32. 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 32. 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 32. The Average Pruritus NRS is included in the investigator trial file.

10.3.2.4 Patient Days of Topical Treatment Use

Subjects will assess their use of topical AD treatment use over the past 24 hours using a response scale ('yes', 'no'). Subjects will complete the Patient Days of Topical Treatment Use as part of an eDiary each day in the morning from baseline (Week 0 [visit 3]) until Week 32. The Patient Days of Topical Treatment Use is included in the investigator trial file.

10.3.2.5 Patient Global Impression of Bother

The 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 32. The PGI-B is included in the investigator trial file.

10.3.2.6 Patient Global Impression of Severity

The 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 32. The PGI-S is included in the investigator trial file.

10.3.2.7 Patient-Oriented Eczema Measure

The POEM is a validated questionnaire used to assess disease symptoms in atopic eczema patients in both clinical practice and clinical trials (30). The tool consists of 7 items each addressing a specific symptom (itching, sleep, bleeding, weeping, cracking, flaking, and dryness). Subject will score how often they have experienced each symptom over the previous week on a 5-point categorical response scale (0 = 'no days'; 1 = '1 to 2 days'; 2 = '3 to 4 days'; 3 = '5 to 6 days'; 4 = 'every day'). The total score is the sum of the 7 items (range: 0 to 28) and reflects disease-related morbidity; a high score is indicative of a worse disease severity. The POEM will be completed electronically on the device supplied to the trial site according to the schedule of procedures (Section 4). The POEM is included in the investigator trial file.

10.3.2.8 Dermatology Life Quality Index

The DLQI is a validated questionnaire with content specific to those with dermatology conditions. It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their HRQoL over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment (31). Each item is scored on a 4-point Likert scale (0 = 'not at all⁄not relevant'; 1 = 'a little'; 2 = 'a lot'; 3 = 'very much'). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor HRQoL. The DLQI will be completed electronically on the device supplied to the trial site according to the schedule of procedures (Section 4). The DLQI is included in the investigator trial file.

10.3.2.9 EQ-5D-5L

The EQ-5D-5L is a standardised measure of health status developed by the EuroQol group to provide a simple, generic measure of health for clinical and economic appraisal (32). The EQ-5D-5L is a self-administered questionnaire used to assess health status 'today' and is divided into 2 sections: The first section includes 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression); each dimension will be assessed by the

subject using a 5-point scale ('no problems', 'slight problems', 'moderate problems', 'severe problems', and 'extreme problems'). The second section consists of a vertical visual analogue scale anchored at 0 ('the worst health you can imagine') and 100 ('the best health you can imagine'). The EQ-5D-5L will be completed electronically on the device supplied to the trial site according to the schedule of procedures (Section 4). The EQ-5D-5L is included in the investigator trial file.

10.3.2.10 Hospital Anxiety and Depression Scale

The HADS is a Likert-scale tool widely used to detect states of anxiety and depression in a general hospital setting (33). The tool consists of 14 items that assess the subject's anxiety (7 items) and depression (7 items) during the last week. Each question is scored from 0 to 3, with high scores indicating a poor state. The HADS will be completed electronically on the device supplied to the trial site according to the schedule of procedures (Section 4). The HADS 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 schedule of procedures (Section 4). Vital signs will be measured in supine position following at least 5 minutes' rest.

For the first 3 IMP dosing visits in both the initial treatment period (i.e., Weeks 0, 2, and 4) and the continuation treatment period (i.e. Weeks 16, 18, and 20), subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 30 minutes with vital signs taken at 30 minutes or until stable, whichever is later (Section 9.1.3.1).

If an abnormal vital sign at screening is considered by the investigator to be clinically significant, it will be at 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. 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 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.

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 schedule of procedures (Section 4).

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

Clinically significant abnormal physical examination findings at the first screening visit will be documented as medical history in the eCRF. If an abnormal finding 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.

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 schedule of procedures (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.

Clinically significant abnormal ECG findings at the first screening visit will be documented as medical history in the eCRF. If an abnormal ECG finding 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.

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 schedule of procedures 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 schedule of procedures in Section 4.

Note that pregnant subjects must discontinue the IMP and NIMP immediately (Section 9.7.1).

10.4.5 Laboratory testing

The following safety samples will be analysed by a central laboratory: chemistry, haematology, serology, and serum pregnancy, see Panel 9 for an overview of the individual laboratory parameters assessed in this trial. 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 schedule of procedures (Section 4).

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.

Panel 9 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 Haematocrit Haemoglobin 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 9.1.3.1).
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.

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

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

Clinically significant abnormal laboratory findings at the first screening visit will be documented as medical history in the eCRF. If an abnormal finding 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.

10.4.6 Pharmacokinetic assessments

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

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 schedule of procedures (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 of ADA will be analysed by a laboratory using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titre determination and will be analysed for the presence of neutralising antibodies (nAB). Details of the analytical method used will be described in 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 Estimate of total blood volume collected

Blood samples will be drawn for safety (chemistry, haematology, and serology), PK, and ADAs. The total volume of blood to be withdrawn is approximately 180 mL which is less than the volume of blood drawn during a blood donation (approximately 500 mL).

11 Adverse events

AEs and SAEs are defined in Appendix 1: Definitions of adverse events and serious adverse events.

Classification of AEs in terms of severity, causality and outcome are defined in Appendix 2: Classification of adverse events.

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 (ICF) until completion of the clinical trial (defined as the safety follow-up visit 16 weeks after last injection of IMP). For subjects entering the long-term extension trial (LP0162-1337, ECZTEND), any (S)AE with onset before the final visit in LP0162-1339 should be reported in LP0162-1339. 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.

Clinically significant abnormal findings related to vital signs, physical examination, ECGs, or laboratory tests after the first screening visit must be reported as an AE in accordance with Section 11.2; also see Sections 10.4.1 (vital signs), 10.4.2 (physical examination), 10.4.3 (ECGs), and 10.4.5 (laboratory tests) for further details.

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 eCRF and should be described in the following manner:

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

The *duration* of the AE must be reported by the start date and stop date of the event. In addition, it must be recorded whether the AE started prior to start of IMP.

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

Action taken with trial treatment: Any action taken with IMP or NIMP (TCS) 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 1: Definitions of adverse events and serious adverse events.

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 or IMP device, causal relationship to NIMP, 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 at Week 46) 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.

For the NIMP (mometasone furoate, 0.1% cream) the latest version of the approved label 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 9.7.1).

11.5 Reporting of other events

11.5.1 Adverse events of special interest

The events listed in Panel 10 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 10 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.
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 eCRF. 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 9.10.

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 trial 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.*" (34).

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 369 subjects will be randomised 2:1 to initial treatment in this trial (246 subjects in the tralokinumab+TCS arm; 123 subjects in the placebo+TCS arm).

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.

The null hypothesis for the first primary endpoint is that there is no difference at Week 16 in obtaining IGA 0/1 between tralokinumab+TCS and placebo+TCS. The null hypothesis for the second primary endpoint is that there is no difference at Week 16 in obtaining EASI75 between tralokinumab+TCS and placebo+TCS. Each hypothesis will be tested against the 2-sided alternative that there is a difference between the 2 treatment groups.

For the single endpoint IGA 0/1 at Week 16, a sample size of 369 subjects randomised 2:1 will provide 90% power to detect a difference between the 2 arms, assuming response rates of 30% for tralokinumab+TCS and 15% for placebo+TCS. For the single endpoint EASI75 at Week 16, a sample size of 369 will provide a nominal power >99.9% to detect a difference between tralokinumab+TCS and placebo+TCS, assuming EASI75 response rates of 40% and 15%, respectively. The combined power for demonstrating a significant difference for both endpoints is therefore effectively also 90% with a sample size of 369 subjects, even when assuming no correlation between the 2 primary endpoints. In all cases, the evaluations will be made with a 2-sided 5% significance level.

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. 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, 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 the inclusion criteria no. 3, 6, 7, and 8.

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 continuation treatment analysis set will be defined as subjects in the full analysis set who have not withdrawn from trial prior to or at the Week 16 visit (visit 11).

A continuation treatment safety analysis set will be defined as subjects who are exposed to IMP at or after the Week 16 visit (visit 11).

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 and continuation treatment. For all randomised subjects and for subjects in the continuation treatment analysis set, 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.

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 continuation treatment 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) and continuation treatment safety analysis set (continuation 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

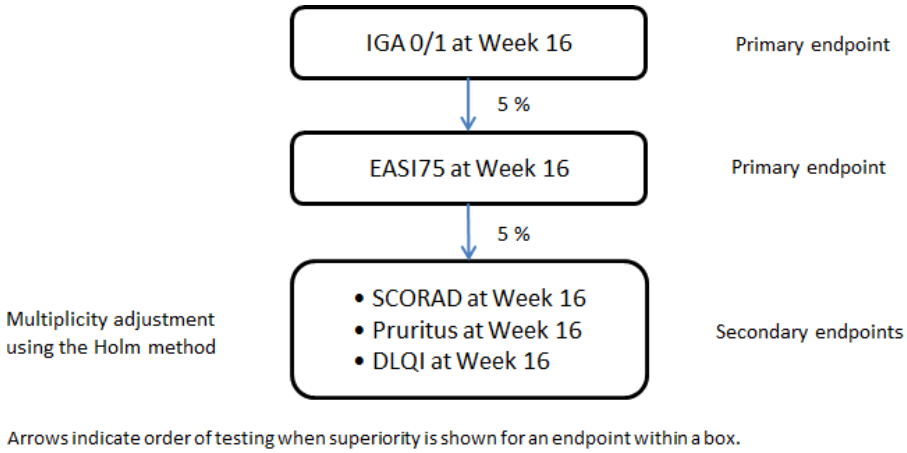
Adherence to treatment regimen will be recorded in the eCRF. The log of drug administration may be used as source. If any complications or deviations in administration are observed, these will be described as protocol deviations.

Adherence will be presented for the safety analysis set (initial treatment) and for the continuation treatment safety analysis set (continuation treatment) for each treatment group.

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 treatment period will follow the hierarchical testing procedure outlined in Panel 11. The hypothesis relating to a specific endpoint cannot be rejected unless all hypotheses relating to endpoints earlier in the hierarchy are also rejected.

Panel 11 Testing procedure for primary and secondary endpoints



Abbreviations: DLQI, Dermatology Life Quality Index; EASI75, at least 75% reduction in Eczema Area and Severity Index score; IGA, Investigator's Global Assessment.

The procedure will be as follows:

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

If both these tests are significant, the 5% significance level (alpha) will be propagated to the three secondary endpoints: SCORAD at Week 16, Pruritus at Week 16, and DLQI at Week 16. The evaluations of the three secondary endpoints between tralokinumab+TCS and placebo+TCS will use the Holm method (35) for 3 ordered p-values at a 5% significance level to adjust for multiplicity.

12.3.5 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 Primary estimand: 'composite'

The primary estimand for the primary endpoints will be:

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

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

Primary analysis for the primary estimand

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

The difference in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test stratified by region (Europe and North America) 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+TCS and placebo+TCS 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 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.

12.3.5.2 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+TCS with no rescue medication as compared to a treatment regimen with placebo+TCS 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=111099).
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=290997).
2. An 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=111099).
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 (Europe and North America) 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+TCS 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+TCS arm as well as the placebo+TCS arm will be imputed from observed data in the placebo+TCS 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.

12.3.5.3 Tertiary estimand: 'treatment policy'

The tertiary estimand for the primary endpoints will be:

- Treatment difference in response rate after 16 weeks between tralokinumab+TCS and placebo+TCS 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+TCS and additional rescue medication as compared to a treatment regimen with placebo+TCS 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.

12.3.6 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 (Day -6 to 0) 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.

12.3.6.1 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+TCS with no rescue medication as compared to a treatment regimen with placebo+TCS 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+TCS and placebo+TCS 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+TCS arm will resemble data from subjects from the placebo+TCS 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+TCS arm as well as the placebo+TCS arm will be imputed from the placebo+TCS 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=290997).

2. For each of the 100 copies of the dataset, an ANCOVA model will be fitted to the SCORAD value at Week 2 in the placebo+TCS group. The model will include effects of baseline SCORAD as a covariate, and 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+TCS group as well as the tralokinumab+TCS group (seed=111099).
3. For each of the 100 copies of the dataset, missing values at Week 4 will be imputed in the same way as for Week 2. The imputations will be based on a similar ANCOVA model, but with SCORAD value at Week 2 included as an additional covariate. The parameters from the model will be estimated based on data from the placebo+TCS group. The estimated parameters, and their variances, will be used to impute missing values at Week 4 for both treatment groups.
4. This stepwise procedure will then be repeated sequentially for 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.

12.3.6.2 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+TCS and placebo+TCS 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+TCS and additional rescue medication as compared to a treatment regimen with placebo+TCS 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 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+TCS arm who have/have not discontinued treatment prior to Week 16 will resemble data from subjects from the placebo+TCS 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+TCS arm as well as the placebo+TCS arm will be imputed from the placebo+TCS 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.

12.3.7 Analysis of additional secondary endpoints

Initial treatment period

The analysis of the below additional secondary endpoints will be based on the primary analyses of the primary estimand as specified above for the relevant primary dichotomous endpoints and continuous secondary endpoints, respectively.

The following dichotomous additional secondary endpoints will be analysed according to the primary analysis of the primary estimand for the primary endpoints:

- EASI50 at Week 16.
- EASI90 at Week 16.
- SCORAD50 at Week 16.
- SCORAD75 at Week 16.
- Reduction from baseline (Y/N) of DLQI of ≥4 points (in subjects with baseline DLQI ≥4) at Week 16.

The change from baseline to Week 16 in EASI score and the change from baseline to Week 16 in Worst Daily Pruritus NRS weekly average will be analysed according to the primary analysis of the primary estimand for the continuous secondary endpoints.

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

Y = treatment × visit + region + baseline IGA

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

AD flares will be summarised descriptively as the proportion of subjects having had AD flares at Week 16, the number of AD flares from baseline to Week 16, and the rate of AD flares from baseline to Week 16. The rate of AD flares will be defined as the number of AD flares divided by time at risk, where the time at risk for each subject is the time from treatment start to last visit attended up to Week 16.

Continuation treatment period

To support the maintenance objective of the trial, IGA of 0/1 at Week 32 among subjects with IGA of 0/1 at Week 16 and EASI75 at Week 32 among subjects with EASI75 at Week 16, both after initial randomisation to tralokinumab, will be summarised descriptively by treatment group of the continuation treatment period.

To support the maintenance objective of the trial, IGA 0/1, EASI75, EASI50, EASI90, SCORAD75, and SCORAD50, all at Week 32, will be summarised descriptively by treatment group of the continuation treatment period.

12.3.8 Analysis of other endpoints

12.3.8.1 Efficacy related other endpoints

To further pursue the objectives supported by the five Week 16 endpoints in the confirmatory test hierarchy, the same endpoints will be evaluated at each scheduled assessment up to Week 14, including also the weekly average of Worst Daily Pruritus NRS:

- 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 scheduled assessment through Week 4 to 14 in Worst Daily Pruritus NRS (weekly average).
- Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to each scheduled assessment through Week 4 to 14.
- 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 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 in the same analysis that already will be made for the corresponding Week 16 assessments.

12.3.8.2 Patient-reported outcomes

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

The PROs collected daily in the eDiaries (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 initial treatment and continuation treatment. Data from the initial treatment period will be presented for the full analysis set and data from the continuation treatment period will be presented for the continuation treatment analysis set.

The Average Daily Pruritus NRS collected over the last week prior to baseline (Day -6 to 0) 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 4 from baseline to Week 2 as well as a reduction of at least 3 from baseline to Week 2 will be summarised by treatment group. Furthermore, to investigate itch relief during initial treatment a reduction in Worst Daily Pruritus NRS weekly average of at least 3 from baseline to Week 16 will be summarised. These three endpoints will each be analysed according to the primary analysis of the primary estimand for the dichotomous primary endpoints.

In the subgroup of subjects with either HADS anxiety or HADS depression subscale score ≥8 at baseline, the proportion of subjects with both HADS anxiety 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 ≥4, the proportion of subjects with a reduction in POEM score ≥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 2 in Worst Daily Pruritus NRS weekly average, and the change from baseline to Week 16 in Eczema-related Sleep NRS weekly average, HADS, POEM, and the EQ-5D-5L index will be summarised by treatment group and domain, where

applicable, and analysed according to the primary analysis of the primary estimand for the continuous secondary endpoints. For the Eczema-related Sleep NRS score, the mean over the last 7 days prior to randomisation (Day -6 to 0) will be used as the baseline value.

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.

12.3.9 Analysis of safety

The analyses of safety will be based on the safety analysis set. The reporting of safety data will be presented separately for initial treatment and continuation treatment.

12.3.9.1 Adverse events

To assess the safety of tralokinumab in combination with TCS when used to treat moderate-to-severe AD for 32 weeks, the frequency of AEs and SAEs are included as additional secondary endpoints.

AEs will be coded during the course of the trial according to Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred terms 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 and the number (percentage) of subjects with any treatment-emergent AEs, deaths, SAEs, premature discontinuations from the trial due to AEs, treatment-related AEs and severe AEs will be presented.

The number of AEs and 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 and NIMP (TCS) for each type of AE will be tabulated by treatment group.

Related AEs are defined as AEs for which the investigator has not described the causal relationship to IMP as 'not related'. The number of related AEs and the number of subjects experiencing each type of related AE will be tabulated. The percentage of subjects with related AEs 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 or permanent discontinuation of IMP will be tabulated and listed.

12.3.9.2 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 and the continuation treatment safety analysis set.

12.3.9.3 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 and the continuation treatment 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.

12.3.9.4 Pharmacokinetics

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

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

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.

12.3.9.5 Anti-drug antibodies

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

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

The association of ADA status across the trial (positive vs. negative) with AEs/SAEs may be evaluated. In addition, the association of ADA titres (≥ median titre in positive subjects versus < median titre) with AE/SAEs may be evaluated for ADA-positive treated subjects only. The ADA-positive subjects across the trial may also be divided into persistent positive versus transient positive. A subject will be considered as persistent positive if he/she has positive ADA 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.

All ADA positive subjects with titre information will be listed.

12.3.10 Interim analysis

No interim analysis is planned.

12.3.11 Analysis of data up to Week 32

To support submission for marketing approval, a 32-week analysis will be performed on data up to Week 32. All analyses pertaining to efficacy endpoints will be final in this 32-week

analysis and will be included in a CTR in the original submission. No adjustments in significance level of the primary and secondary analyses will therefore be applied. Blinding of investigators and other site staff involved in the conduct of the trial will be maintained for the entire duration of the trial (please refer to Section 9.2.1 for further details).

The safety results for the safety follow-up period (Week 32 to 46) for all subjects will be included in an addendum to the original CTR and will be submitted as part of the 120-Day Safety Update.

12.3.12 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.

12.3.13 Handling of missing values

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

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Appendix 1: Definitions of adverse events and serious adverse events

Adverse event definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH Harmonized Tripartite Guideline for GCP, E6 [R1]).

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavourable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures unless these were planned before 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 fulfil the criteria for being an SAE but should be documented in the subject's medical record.
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.

or

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

Appendix 2: Classification of adverse events

Severity

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

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

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

Causality

The *causal relation* of the AE to the use of the IMP should be described in terms of probable, possible or not related according to the 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.

Similarly, the causal relationship to the use of NIMP (TCS) should also be evaluated using the same definitions as for the IMP (i.e. probably, possibly, or not related to NIMP).

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 3: Trial governance considerations

Appendix 3A: Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Current version of applicable ICH 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 3B: 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 applicable.

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 3C: Subject and data confidentiality

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

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

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

Case report forms

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

The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRFs used. This signature information will be kept in the audit trail

and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require the re-signature by the investigator. The person making the change to the data, and the date, time and reason for the change will be identified in the audit trail.

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 with tralokinumab or placebo for 32 weeks.
- Other relevant medical information.

Trial monitoring

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

The monitoring visit intervals will depend on the trial site's recruitment rate, 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

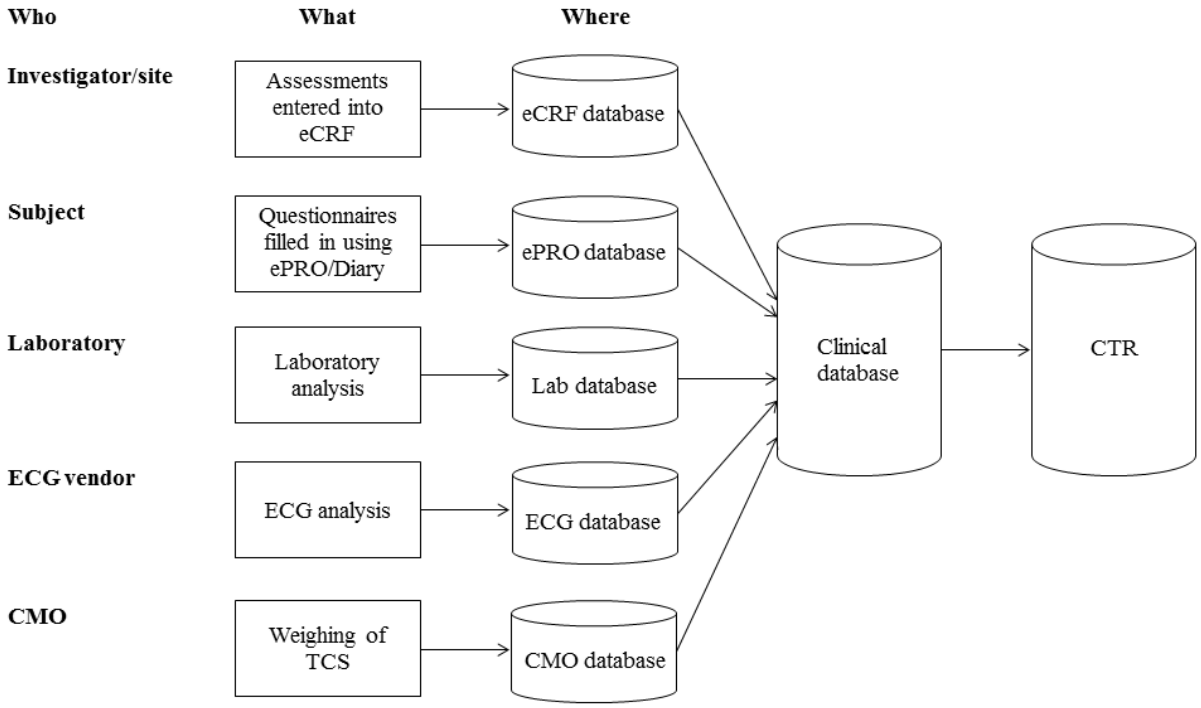
Subject data should be entered into the eCRF as soon as possible after each visit in accordance with the requirements described in the Clinical Trial Agreement, if applicable. Queries for discrepant data will be generated automatically by the system upon entry or manually by the CRA, sponsor's medical 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 12.

Panel 12 Transmission of electronic data



Abbreviations: CMO, contract manufacturing organisation; CTR, clinical trial report; ECG, electrocardiogram; eCRF, electronic case report form; ePRO, electronic patient-reported outcome; Lab, laboratory; TCS, topical corticosteroid.

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 3E: 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 3F: Insurance

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

Appendix 3G: Financial disclosure

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

Appendix 3H: Trial and site closure

Premature termination of trial or trial site

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, LEO's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- 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 3I: 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 4: Hanifin and Rajka (1980) diagnostic criteria for AD (21)

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

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

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

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

Appendix 5: Guidance for anaphylaxis diagnosis (24)

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

Clinical criteria for diagnosing anaphylaxis

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

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

AND AT LEAST ONE OF THE FOLLOWING:

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

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   - Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Appendix 6: 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

International coordinating investigator
Associate Professor Jonathan Silverberg, MD, PhD, MPH, Departments of Dermatology, Preventive Medicine and Medical Social Sciences, Northwestern University Feinberg School of Medicine, United States

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 laboratory	ACM Global Central Laboratory 23 Hospital Fields Road, York YO10 4DZ United Kingdom
Bioanalysis of PK and ADA samples	Covance Laboratories Ltd. Otley Road, Harrogate, North Yorkshire HG3 IPY United Kingdom
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
Emergency unblinding CRO	C3i, Inc 25 Lindsley Drive, Morristown, NJ 07960 United States of America

Appendix 7: Protocol amendment history

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

Amendment 2 (10-Apr-2018)

This amendment is considered 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 a change in the procedure for safety monitoring of the trial subjects in relation to the administration of investigational medicinal product (IMP). This change is endorsed by the Safety Review Board at LEO Pharma A/S, following an evaluation of safety data from:

- 1 completed phase 2b trial with tralokinumab in AD (trial D2213C00001): 153 subjects exposed to tralokinumab (12-week treatment period).
- 2 ongoing phase 3 trials with tralokinumab in AD (trial LP0162-1325 and LP0162-1326): 1089 subjects treated for ≥ 4 weeks (blinded safety data evaluated, cut-off: 02-Mar-2018).
- 2 completed phase 3 trials with tralokinumab in asthma (trial D2210C00007 and D2210C00008): 1627 subjects exposed to tralokinumab (52-week treatment periods).

Note: The table below describes the changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has a ~~line through it~~).

Section no. and name	**Description of change**	**Brief rationale**
Section 4 Schedule of trial procedures	The visit window for screening visit 2 has been corrected from ±3 to -3 days. The visit window for baseline (visit 3) has been set to 'Not applicable'.	To ensure that subjects will have no less than 14 days between screening and baseline. As all subsequent visits should be planned to maintain the visit schedule relative to baseline (as already stated in Section 4).
	Footnote 6 to Panel 2: For the first 3 IMP dosing visits (visits 3 to 5) and after re-randomisation (visits 11 to 13), subjects will be monitored after IMP administration for immediate drug reactions for a minimum of **30 minutes** ~~2 hours~~ with vital signs taken **at** ~~every~~ 30 minutes or until stable, whichever is later (see Section 9.1.3.1).	Based on the endorsement by the Safety Review Board at LEO Pharma A/S, following an evaluation of the safety data from 3 completed and 2 ongoing trials with tralokinumab.
Section 7.1 Overall trial design	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 into the eDiary during the 2 weeks before randomisation **(including the data collected on the day of the baseline visit [visit 3])** will be used to calculate baseline values of the patient reported outcomes (PROs).	Clarification of how the baseline values for the PROs will be calculated.
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.

Section no. and name	**Description of change**	**Brief rationale**
Section 9.1.3.1 Administration of IMP Section 10.4.1 Vital Signs	For the first 3 IMP dosing visits (visits 3 to 5) and after re-randomisation (visits 11 to 13), subjects will be monitored after IMP administration for immediate drug reactions for a minimum of **30 minutes** ~~2 hours~~ with vital signs taken **at** ~~every~~ 30 minutes or until stable, whichever is later	Based on the endorsement by the Safety Review Board at LEO Pharma A/S, following an evaluation of the safety data from 3 completed and 2 ongoing trials with tralokinumab.
Section 9.5 Prohibited medication and procedures	The following medications are prohibited during the trial from randomisation through safety follow-up (Week 0 to 46): • **Other topical medications used for the treatment of AD other than the supplied TCS, except lower potency TCS or TCI which may be used at the investigator's discretion on areas of the body where use of the supplied TCS is not advisable.** • Investigational agents other than tralokinumab. • Immunoglobulin or blood products. • etc.	Clarification of which topical medications (other than the supplied TCS) are to be considered disallowed during the trial.
Section 12.3.6 Analysis of secondary endpoints	Subject reported worst daily itch over the last week prior to baseline **(Day -6 to 0)** will be used to calculate the baseline itch (see also inclusion criterion no. 9).	Clarification of how the baseline values for the PROs will be calculated for the analyses.
Section 12.3.8.2 Patient-reported outcomes	The Average Daily Pruritus NRS collected over the last week prior to baseline **(Day -6 to 0)** will be used to calculate the baseline average daily itch. For the Eczema-related Sleep NRS score, the mean over the last 7 days prior to randomisation **(Day -6 to 0)** will be used as the baseline value.	

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

Amendment 1 (15-Dec-2017)

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

Overall rationale for the amendment

The reason for the amendment is an operational change related to the non-investigational medicinal product (TCS) to be handed out to the subjects. The need for this change was identified after finalisation of the original 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 no. and name	Description of change	Brief rationale
Protocol synopsis Section 2 Trial identification	ClinicalTrials.gov identifier (**NCT03363854**) added.	As the identifier has become available since the time of protocol finalisation.
Protocol synopsis Section 9.1.2 Non-investigational medicinal product Section 9.1.3.2 Administration of	The mometasone furoate 0.1% cream will be provided in kit sizes of 180–225 g (instead of 200 g) every 2 weeks.	To provide flexibility across regions due to differences in the available pack sizes of mometasone furoate (0.1% cream).

Section no. and name	**Description of change**	**Brief rationale**
NIMP Section 9.8.1.2 Labelling and packaging of NIMP		
Section 8.2 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 11.3.2 LEO reporting responsibilities	For the NIMP (mometasone furoate**, 0.1% cream**) the latest version of the approved label must be used ~~(see the Elocon® Summary of Product Characteristics [Europe], December 2015 edition and subsequent updates; the Elocon® Prescribing Information [USA], April 2013 edition and subsequent updates; or the Elocom® Product Monograph [Canada], May 2014 edition and subsequent updates)~~.	Specification that mometasone furoate will be supplied as 0.1% cream. Details regarding the approved labels have been omitted.
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 3D.

Signature Page for TMF-000005673 v4.0

Reason for signing: Approved	Manage Verdict(s) Name: PPD Capaci Date of signature: 29-Aug-2018 20:22:18 GMT+0000

Reason for signing: Approved	Manage ver Verdict(s) Name: PPD Capaci Date of signature: 30-Aug-2018 09:14:53 GMT+0000

Reason for signing: Approved	Manage s) Name: PPD Capaci Date of signature: 31-Aug-2018 05:51:34 GMT+0000

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