Cover Page

Official title: A Randomised, Double-blind, Placebo-controlled Trial to Evaluate the Effect of Tralokinumab on Vaccine Antibody Responses in Adults With Moderate-to-severe Atopic Dermatitis Who Are Candidates for Systemic Therapy
LEO Pharma number: LP0162-1341
NCT number: NCT03562377
Date: 23-Apr-2018

Clinical Trial Protocol

LP0162-1341

Vaccine responses in tralokinumab-treated atopic dermatitis

ECZTRA 5 (ECZema TRAlokinumab trial no. 5)

Phase 2 – Vaccine response trial

A randomised, double-blind, placebo-controlled trial to evaluate the effect of tralokinumab on vaccine antibody responses in adults 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:**	**LP0162-1341**
	Date:	**23-Apr-2018**
	EudraCT no:	**Not applicable**
	Version:	**1.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

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

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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 signatory investigator

The signatory investigator approves the clinical trial protocol by manually signing the Signatory Investigator Clinical Trial Protocol Approval Form, which is a separate document appended to this document.

The following person has approved this clinical trial protocol:

Joseph F. Merola, MD, MMSc
Signatory investigator

Acknowledgement statement investigator(s)

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

Table of contents

List of panels

List of abbreviations

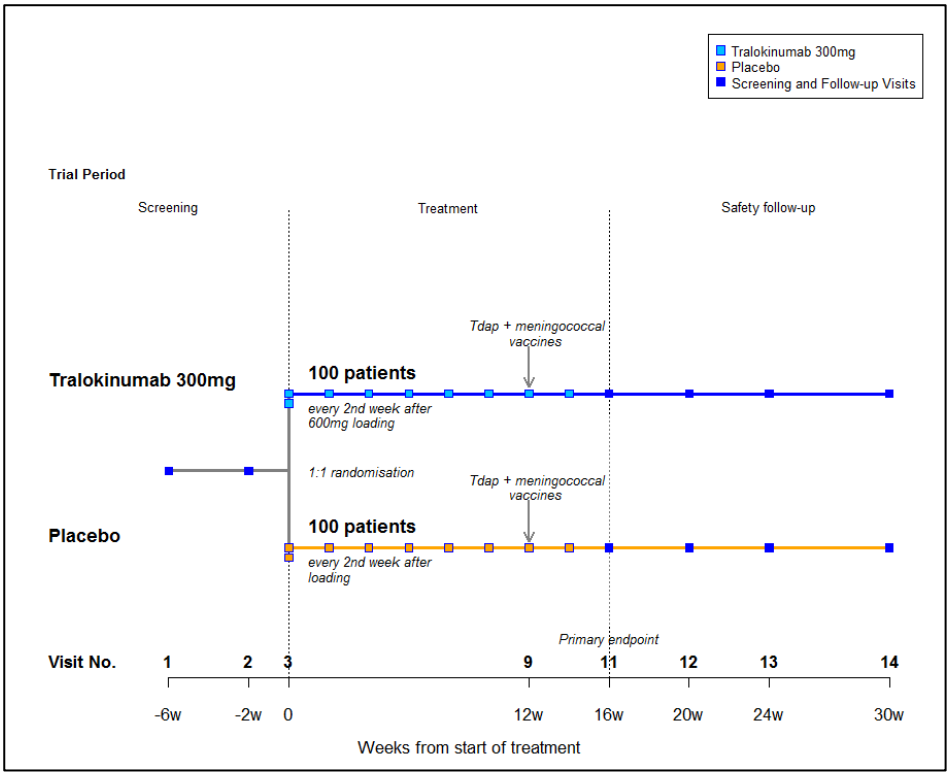
AD	atopic dermatitis
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BSA	body surface area
CCL22	C-C motif chemokine 22
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence 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
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL 5-Dimension Health Questionnaire 5 Level
FAS	full analysis set
FDA	Unites States Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HCP	healthcare professional
HIV	human immunodeficiency virus
HRQoL	health-related quality of life

ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
LEO	LEO Pharma A/S
Lf	limit of flocculation
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
nAB	neutralising antibodies
PCR	polymerase chain reaction
PD	pharmacodynamics
PDE-4	phosphodiesterase 4
PK	pharmacokinetics
POEM	Patient-Oriented Eczema Measure
Q2W	every 2 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
SDTM	study data tabulation model
SOC	system organ class
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
Tdap	tetanus, diphtheria, and acellular pertussis
Th2	T-helper-2

ULN	upper limit of normal
US	United States of America
UV	ultraviolet
WHO	World Health Organization

1 Protocol synopsis

<table>
<tr><td>Trial ID
IND no.
FDA center</td><td>LP0162-1341
123797
CDER</td></tr>
<tr><td>Title of trial</td><td>A randomised, double-blind, placebo-controlled trial to evaluate the effect of tralokinumab on vaccine antibody responses in adults with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic therapy.</td></tr>
<tr><td>Short title of trial</td><td>Vaccine responses in tralokinumab-treated atopic dermatitis</td></tr>
<tr><td>Main objectives and endpoints</td><td>
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary objective</td><td>Primary endpoints</td></tr>
<tr><td>To demonstrate non-inferiority of tralokinumab versus placebo with respect to immune responses to concomitantly administered vaccines.</td><td>• Positive anti-tetanus response at Week 16 (3-fold IgG increase compared to Week 12 if IgG ≤1.0 IU/mL at Week 12; or IgG ≥2.5 IU/mL if IgG >1.0 IU/mL at Week 12)
• Positive anti-meningococcal response at Week 16 (IgG ≥3.0 mcg/mL with at least a 3-fold increase compared to Week 12)</td></tr>
<tr><td>Secondary objective</td><td>Secondary endpoints</td></tr>
<tr><td>To evaluate efficacy of tralokinumab concomitantly administered with vaccines.</td><td>• Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) at Week 16[1]
• At least 75% reduction in Eczema Area and Severity Index (EASI75) at Week 16[2]</td></tr>
<tr><td>Additional secondary objective</td><td>Additional secondary endpoints</td></tr>
<tr><td>To evaluate safety and tolerability of tralokinumab concomitantly administered with vaccines.</td><td>• Number of adverse events (AEs)
• Presence of anti-drug antibodies</td></tr>
</table>
[1] The IGA is an instrument used in clinical trials to rate the severity of the subject's global AD and is based on a 5-point scale ranging from 0 (clear) to 4 (severe).
[2] The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. The EASI is a composite index with scores ranging from 0 to 72, with higher values indicating more severe and/or more extensive condition.
</td></tr>
<tr><td>Final collection of data for the primary endpoints</td><td>Week 16</td></tr>
</table>

Trial design	The trial will consist of a screening period of 2 to 6 weeks (Weeks -6/-2 to 0), a treatment period of 16 weeks (Weeks 0 to 16), and a 14-week off-treatment follow-up period for the assessment of safety (Weeks 16 to 30). Eligible subjects may transfer to the open-label, long-term ECZTEND trial (LP0162-1337) at Week 16 or later. Subjects will be randomised in a 1:1 ratio to receive 300 mg (2 mL) of tralokinumab or placebo (2 mL) every 2 weeks (Q2W) following a loading dose of 600 mg (4 mL) or placebo (4 mL) on Day 0. Randomisation will be stratified by baseline disease severity (IGA 3 or 4). The last administration of IMP will occur at Week 14. Subjects will each receive 1 dose of combined tetanus, diphtheria, and acellular pertussis (Tdap) vaccine and 1 dose of meningococcal vaccine given intramuscularly at Week 12. The primary endpoints will be assessed at Week 16, and the final safety assessment will be conducted at Week 30 for those not rolling over to the ECZTEND trial (LP0162-1337). 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).  Tdap, tetanus, diphtheria, and acellular pertussis; w, weeks.
Main assessments	<u>Assessments of vaccine-specific antibody response</u> Anti-tetanus response, anti-meningococcal response. <u>Safety assessments</u> Vital signs, physical examination, electrocardiograms, laboratory testing, pharmacokinetics, anti-drug antibodies, and adverse event reporting.

	Efficacy: investigator assessments IGA, EASI, and Scoring Atopic Dermatitis (SCORAD). Efficacy: subject assessments 4 patient-reported outcomes will be completed by the subjects at the site during trial visits: Dermatology Life Quality Index (DLQI), EuroQoL 5-Dimension Health Questionnaire 5 Level (EQ-5D-5L), Patient-Oriented Eczema Measure (POEM), and Hospital Anxiety and Depression Scale (HADS).
Main criteria for inclusion	• Age 18 to 54 years, both included, at screening • Diagnosis of AD as defined by 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 or for whom topical treatments are otherwise medically inadvisable • AD involvement of ≥10% body surface area at screening and baseline according to component A of SCORAD • An EASI score of ≥12 at screening and 16 at baseline • An IGA score of ≥3 at screening and at baseline • Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation
Main criteria for exclusion	• Subjects for whom administration of the meningococcal vaccine provided in this trial is contraindicated or medically inadvisable, according to local label of the vaccine • Subjects for whom administration of the tetanus, diphtheria, and pertussis vaccine provided in this trial is contraindicated or medically inadvisable, according to local label of the vaccine • Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis • Use of tanning beds or phototherapy within 6 weeks prior to randomisation • Treatment with immunosuppressive/immunomodulating medications and/or systemic corticosteroids within 4 weeks prior to randomisation • Treatment with the topical medications topical corticosteroids (TCS), topical calcineurin inhibitor (TCI) or phosphodiesterase 4 (PDE-4) inhibitor within 2 weeks prior to randomisation • Receipt of any vaccine (except influenza virus vaccines) within 3 months prior to screening, any meningococcal vaccine within 1 year prior to screening, or any tetanus-, diphtheria-, or pertussis-containing vaccine within 5 years prior to screening • Receipt of any marketed or investigational biologic agents (e.g., cell-depleting agents or dupilumab) within 6 months prior to randomisation or until lymphocyte counts return to normal, whichever is longer • History of any active skin infection within 1 week prior to randomisation • History of a clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to randomisation

Investigational medicinal products	Tralokinumab (human recombinant IL-13 monoclonal antibody) 150 mg/mL solution for subcutaneous injection in an accessorised pre-filled syringe, 1.0 mL fill volume. Each kit contains 1 syringe. Placebo Placebo solution for subcutaneous injection in an accessorised pre-filled syringe, 1.0 mL fill volume. Each kit contains 1 syringe. Tdap vaccine Combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine. Suspension for injection in 0.5 mL single dose pre-filled syringes. Meningococcal vaccine Meningococcal (groups A, C, Y and W-135) polysaccharide diphtheria toxoid conjugate vaccine. Solution for injection in 0.5 mL single dose vials.
Duration of treatment	Each subject's trial participation will be up to 36 weeks: screening period (including washout, if applicable) up to 6 weeks, treatment period of 16 weeks, and follow-up period of 14 weeks (subjects may enter the long-term extension trial, ECZTEND, at any time during the safety follow-up period).
Number of subjects	A total of 200 subjects will be randomised 1:1 to tralokinumab 300 mg Q2W or placebo.
Number and distribution of trial sites	Approximately 40 sites in the US and Canada.
Statistical methods	Primary endpoints: The difference in response rates between treatment groups will be calculated using the Mantel-Haenszel estimate of the risk difference stratified by baseline disease severity (IGA 3 or 4) together with the 95% confidence intervals. Non-inferiority of tralokinumab will be demonstrated if the lower limit of the 95% confidence interval is greater than -25%. The per protocol analysis will be considered the primary analysis. Analyses will be based on observed data; thus missing data will not be imputed. Secondary endpoints: The difference in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test stratified by baseline disease severity (IGA 3 or 4). The primary analysis will be based on the full analysis set. Subjects with missing data or subjects who receive rescue medication prior to Week 16 will be considered as non-responders in the analysis. Testing strategy The primary and secondary endpoints will be evaluated hierarchically in the order shown in Panel 13. The hypothesis relating to a specific endpoint cannot be rejected unless all hypotheses relating to endpoints earlier in the hierarchy are also rejected. For the primary endpoints a non-inferiority hypothesis will be tested using a non-inferiority limit of -25%. For the secondary endpoints a superiority hypothesis will be tested. All hypotheses will be tested at a one-sided 2.5% significance level. For the primary endpoints, the null hypothesis will be rejected if the two-sided 95% confidence interval for the difference in immune response rate lies entirely to the right of the non-inferiority limit (-25%). For the secondary endpoints, the hypotheses will be tested by calculating the two-sided 95% confidence intervals and p-value.

Signatory investigator	Joseph F. Merola, MD, MMSc Brigham and Women's Hospital, Boston, MA, USA
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

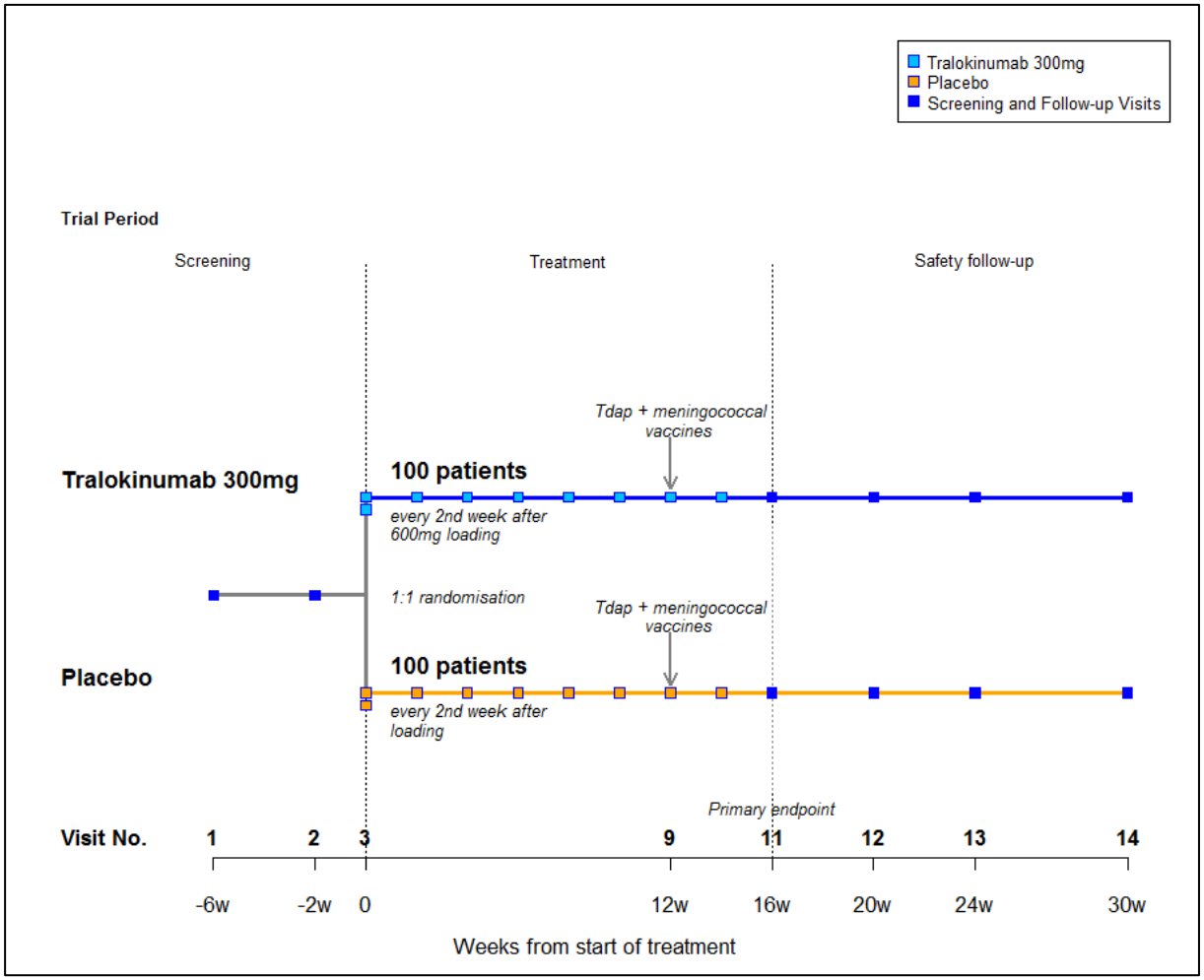
2 Trial identification

IND number: 123797

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

3 Schematic of trial design

Panel 1: Trial design



Tdap, tetanus, diphtheria, and acellular pertussis; w, weeks.

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

	Screening		Treatment period									Follow-up[2,3]			Uns. visit[6] (if appl.)	Early term.[5,7] (if appl.)	Nominal Week 16 visit[8] (if appl.)	References (protocol section)
Visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[2]**	**12[4]**	**13[4]**	**14[5]**			**11x**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**30**			**16**	
Visit window (days)[9]	**±3**	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**NA**	**NA**	**±3**	
Trial population and eligibility																		
Informed consent[10]	X																	Appendix 3B
Subject eligibility	X		X															8.2;8.3
Treatments and randomisation																		
Initiation of emollient (background treatment)[11]		X																9.4
Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X	X	X[6]	X	X	9.6
Concurrent procedures	X		X	X	X	X	X	X	X	X	X	X	X	X	X[6]	X	X	9.6
Randomisation			X															9.3
IMP (tralokinumab/placebo) administration, compliance			X[12]	X[12]	X[12]	X	X	X	X[13]	X								9.2.1;9.8.4
IMP (Tdap vaccine) administration, compliance									X[13]									9.2.2;9.8.4
IMP (meningococcal vaccine) administration, compliance									X[13]									9.2.2;9.8.4

Panel 2: Schedule of trial procedures (continued)

	Screening		Treatment period									Follow-up[2,3]			Uns. visit[6] (if appl.)	Early term.[5,7] (if appl.)	Nominal Week 16 visit[8] (if appl.)	References (protocol section)
Visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[2]**	**12[4]**	**13[4]**	**14[5]**			**11x**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**30**			**16**	
Visit window (days)[9]	**±3**	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**NA**	**NA**	**±3**	
Investigator assessments at screening/baseline only																		
C-SSRS	X																	11.2.5
Demographics	X																	11.2.1
Demographics (age)[14]	X		X															11.2.1
Medical history	X																	11.2.2
Height and weight			X															11.2.3
Body surface area involvement	X[15]		X[15]															11.2.4
Investigator assessments of efficacy																		
SCORAD	X		X	X	X	X	X	X	X	X	X				X[6]	X	X	11.3.3
IGA	X		X	X	X	X	X	X	X	X	X				X[6]	X	X	11.3.1
EASI	X		X	X	X	X	X	X	X	X	X				X[6]	X	X	11.3.2
Subject assessments of efficacy																		
DLQI			X	X	X	X	X		X		X				X[6]	X	X	11.3.4.1
EQ-5D-5L			X		X		X		X		X				X[6]	X	X	11.3.4.2
POEM			X	X	X	X	X		X		X				X[6]	X	X	11.3.4.3
HADS			X		X		X		X		X				X[6]	X	X	11.3.4.4

Panel 2: Schedule of trial procedures (continued)

	Screening		Treatment period									Follow-up[2,3]			Uns. visit[6] (if appl.)	Early term.[5,7] (if appl.)	Nominal Week 16 visit[8] (if appl.)	References (protocol section)
Visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[2]**	**12[4]**	**13[4]**	**14[5]**			**11x**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**30**			**16**	
Visit window (days)[9]	**±3**	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**NA**	**NA**	**±3**	
Investigator assessments of safety																		
Vital signs	X		X[12]	X[12]	X[12]	X	X	X	X	X	X			X	X[6]	X		11.4.1
Physical examination	X		X				X				X			X	X[6]	X		11.4.2
ECG	X		X								X			X	X[6]	X		11.4.3
Chemistry, haematology, IgE (central laboratory)	X[16]		X		X		X		X		X			X	X[6]	X		11.4.5
Serum pregnancy test; hepatitis B, C; HIV (central laboratory)	X																	11.4.4; 11.4.5
Urine pregnancy test			X		X		X		X		X			X	X[6]	X		11.4.4
Urinalysis	X		X		X		X		X		X			X	X[6]	X		11.4.5
Anti-drug antibodies			X		X						X			X	X[6]	X		11.4.6
Pharmacokinetics					X						X			X	X[6]	X		11.6
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[6]	X	X	13
Assessment of vaccine antibody response																		
Anti-tetanus response									X		X				X[6,17]	X[18]	X[18]	11.5
Anti-meningococcal response									X		X				X[6,17]	X[18]	X[18]	11.5

1) For subjects who do not require a wash-out, visits 1 and 2 will be combined and screening will be reduced to 2 weeks; hence, these subjects will only attend visit 2 (Week -2) which will include all assessments shown under Week -6. Similarly, for subjects who only require a 2-week wash-out, screening visits 1 and 2 will be combined (Week -2). The screening period has a maximum duration of 6 weeks.
2) Eligible subjects may roll over to the ECZTEND trial at Week 16 or later. See also footnote no. 5.
3) All subjects, except for those who roll over to the ECZTEND trial (LP0162-1337), will have a full 14-week off-treatment safety follow-up period. The safety follow-up period includes 2 telephone contacts and an office visit (end-of-trial visit) at Week 30. Subjects may transfer to the ECZTEND trial at any time during the safety follow-up period.
4) Visit will be conducted as a telephone contact.
5) An end-of-treatment form and end-of-trial form must be completed in the eCRF for all randomised subjects. See Section 11.10 for further details.
6) Assessments and procedures to be performed at an unscheduled visit are left at the investigator's discretion.
7) Subjects who permanently discontinue IMP or withdraw from the trial will be followed up as described in Section 10.3 and will have a final safety follow-up visit 16 weeks after last dose of IMP.
8) Subjects who permanently discontinue IMP prior to Week 16 will also attend the nominal Week 16 visit (visit 11x).
9) If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to baseline.
10) The informed consent form must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations and wash-out of disallowed medications.
11) 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).
12) For the first 3 IMP (tralokinumab/placebo) dosing visits, subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 30 minutes with vital signs taken at 30 minutes or until stable, whichever is later (Section 9.2.1).
13) Since the 2 vaccinations will be given in the upper arms (1 vaccine in each arm), the IMP (tralokinumab/placebo) injections at Week 12 will be given at a different anatomical site (that is, anterior thigh or abdomen).
14) Where it is not allowed to collect the subject's full date of birth per local legislation, the subject's age in years will also be recorded.
15) The total body surface area affected by AD will be assessed by the investigator as component A of SCORAD.
16) IgE not measured at screening.
17) Only to be considered if the unscheduled visit occurs after Week 12 (that is, after administration of the vaccines).
18) Only required if the subject permanently discontinues IMP (tralokinumab/placebo) after Week 12 (that is, after administration of the vaccines).

Appl., applicable; C-SSRS, Columbia-Suicide Severity Rating Scale; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; 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; POEM, Patient Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; Tdap, tetanus, diphtheria, and acellular pertussis; term., termination; uns., unscheduled.

5 Introduction and trial rationale

5.1 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 Th2 pathway with increased skin expression of key Th2 cytokines including 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 CCL22 and recruit more IL-13 expressing Th2 cells, decrease differentiation, and contribute to decreased barrier function (9). IL-13 also drives 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.

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

5.2 Experience with investigational medicinal product

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

In total, 14 clinical trials have been conducted with tralokinumab, with phase 3 development ongoing in AD. Other clinical trials with tralokinumab have been conducted in subjects with asthma, 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 TCS, were treated with 3 different regimens of tralokinumab (45 mg 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 EASI at Week 12 and the percentage of subjects achieving IGA response of 0 (clear) or 1 (almost clear) at Week 12. Secondary endpoints included change from baseline in EASI and SCORAD scores, EASI50, and SCORAD50. In the overall intent-to-treat phase 2b population, an improvement in EASI score at Week 12 was seen in the tralokinumab 300 mg Q2W group versus placebo. 26% of subjects achieved an IGA of 0 or 1 in the tralokinumab 300 mg Q2W group versus 12% in the placebo group. The most commonly reported causally related treatment emergent adverse event was upper respiratory tract infection (6 [3.9%] subjects in the combined tralokinumab group (45 mg, 150 mg, and 300 mg) and 2 [3.9%] subjects in the placebo group).

In total, more than 2,343 subjects have been treated with tralokinumab (cut off date: 18-Aug-2017). 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

Tralokinumab blocks IL-13 signalling and thereby modulates the immune system to inhibit the inflammatory Th2 response seen in patients with AD (3, 13, 16, 17); refer also to Section 5.1. This immunomodulation could potentially impair the immune response and compromise immunity in treated patients. Since vaccination programmes are an important part of health maintenance and globally recommended, it is relevant to investigate if tralokinumab affects development of vaccination-induced immune responses (18).

This trial will assess immunisation responses against 2 vaccines (a combined tetanus, diphtheria, and acellular pertussis [hereinafter ‘Tdap’] vaccine and a meningococcal [groups A, C, Y and W-135] polysaccharide conjugated vaccine) in adults with moderate-to-severe AD who are treated with tralokinumab. These 2 standard vaccines have been selected to enable a broader assessment of the effect of tralokinumab on immune activation. The selected types of vaccines are known to result in an immune response involving both T and B cells as well as other key cell types of the immune system.

5.4 Justification for dose

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

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

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

The 300 mg Q2W dose is also used in the ongoing phase 3 trials ECZTRA 1, ECZTRA 2, and ECZTRA 3.

The Tdap and the meningococcal vaccines will be given according to the local labelling, that is, a single intramuscular injection (0.5 mL) of each vaccine.

5.5 Ethical considerations

No children or other vulnerable subjects incapable of giving informed consent will be enrolled in this clinical trial. Furthermore, women who are pregnant, breastfeeding, or trying to become pregnant will not be enrolled in this clinical trial. Women of child-bearing potential have to agree to use a highly effective method of contraception to prevent pregnancy during the clinical trial and until 16 weeks after discontinuation of treatment with the IMP. In

addition, all female subjects of child-bearing potential will have a pregnancy test performed before, during and at end-of-treatment to ensure that no foetuses are exposed to the IMP.

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

In this clinical trial in adult subjects with moderate-to-severe AD who are otherwise healthy, the immunisation responses against 2 vaccines in subjects treated with tralokinumab will be compared to a placebo control group. The choice of placebo as control is appropriate for addressing the objectives of this trial and it will provide information regarding immunisation response and the efficacy and safety of tralokinumab concomitantly administered with vaccines. The Tdap and meningococcal vaccines to be used are standard, marketed vaccines.

Subjects will be under supervision by a dermatologist or allergist every second week during the treatment period, which is more frequent than standard clinical practice. This will ensure that the subject's AD is carefully monitored and treated as needed in this trial. Rescue treatment may be given to the subjects at the investigator's discretion for the duration of the trial. If subjects receive rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs, treatment with IMP will be immediately discontinued. Investigators should only enrol subjects they expect will be able to complete the wash-out of previous AD medications without experiencing intolerable worsening of their AD. Subjects will be informed to contact the investigator if they experience a significant worsening of their AD.

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 ICH 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 vaccine response trial with tralokinumab is regarded as ethically justified and adherent with ethical requirements.

5.6 Benefit/risk assessment

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

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

In clinical trials completed to date tralokinumab was well tolerated. A number of theoretical potential risks have been identified that are described in the current 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 trial procedures in Section 4).
- Close monitoring of subjects during the post-dosing period (at the first 3 IMP dosing visits) as a precautionary measure against hypersensitivity reactions (further details are given in Section 9.2).
- Monitoring of subjects for clinical manifestations that may be associated with the development of specific antibodies to tralokinumab (i.e., immune complex disease).
- Exclusion of subjects with untreated systemic helminth infestations or subjects who have failed to respond to standard of care therapy. Neutralisation of IL-13 might theoretically cause a worsening of parasitic infestation, in particular, prevention of expulsion of gastrointestinal worms (helminths) (20).
- Exclusion of subjects with a history of tuberculosis requiring treatment within 12 months prior to the screening visit.

- Exclusion of subjects with a history of a clinically significant infection (defined as a systemic or serious skin infection requiring parenteral antibiotics, antiviral, or anti-fungal medication; see Section 8.3) within 4 weeks prior to baseline which, in the opinion of the investigator or sponsor's medical expert, may compromise the safety of the subject in the trial.

In conclusion, previous clinical experience with tralokinumab shows no major safety or tolerability concerns and appropriate measures have been instituted in this trial to protect subjects from possible risks that have been previously identified and to closely monitor each subject. The current risk/benefit ratio is favourable and supports the administration of tralokinumab in combination with the 2 vaccines for the purposes of achieving the objectives of this trial.

6 Trial objectives and endpoints

Panel 3: Objectives and endpoints

Objectives	Endpoints
Primary objective	Primary endpoints
To demonstrate non-inferiority of tralokinumab versus placebo with respect to immune responses to concomitantly administered vaccines.	• Positive anti-tetanus response at Week 16 (3-fold IgG increase compared to Week 12 if IgG ≤1.0 IU/mL at Week 12; or IgG ≥2.5 IU/mL if IgG >1.0 IU/mL at Week 12) • Positive anti-meningococcal response at Week 16 (IgG ≥3.0 mcg/mL with at least a 3-fold increase compared to Week 12)
Secondary objective	Secondary endpoints
To evaluate efficacy of tralokinumab concomitantly administered with vaccines.	• IGA score of 0 (clear) or 1 (almost clear) at Week 16 • EASI75 at Week 16
Additional secondary objective	Additional secondary endpoints
To evaluate safety and tolerability of tralokinumab concomitantly administered with vaccines.	• Number of AEs • Presence of anti-drug antibodies
Other objectives	Other endpoints
To evaluate the efficacy of tralokinumab concomitantly administered with vaccines on severity and extent of AD and health-related quality of life.	• EASI50 at Week 16 • EASI90 at Week 16 • Change from baseline to Week 16 in EASI score • SCORAD75 at Week 16 • SCORAD50 at Week 16 • Change from baseline to Week 16 in SCORAD • Change from baseline to Week 16 in DLQI score • Change from baseline to Week 16 in EQ-5D-5L • Change from baseline to Week 16 in POEM • Change from baseline to Week 16 in HADS

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; 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.

7 Trial design

7.1 Overall trial design

Overview

This is a randomised, double-blinded, placebo-controlled, phase 2 trial in adult subjects with moderate-to-severe AD. The primary objective of the trial is to demonstrate non-inferiority of tralokinumab versus placebo with respect to immune response to concomitantly administered Tdap and meningococcal vaccines. The trial will evaluate the percentage of subjects achieving a positive anti-tetanus response at Week 16 and a positive meningococcal response at Week 16.

The trial will consist of a screening period of 2 to 6 weeks (Weeks -6/-2 to 0), a treatment period of 16 weeks (Weeks 0 to 16) and a 14-week off-treatment follow-up period for the assessment of safety (Weeks 16 to 30). The primary endpoints will be assessed at Week 16, and the final safety assessment will be conducted at Week 30 (end-of-trial visit). Eligible subjects may transfer to the open-label ECZTEND trial (LP0162-1337) at Week 16 or later. An overview of the different parts of the trial 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 depends on the washout period defined by the exclusion criteria (Section 8.3). If a washout is not required, screening will be reduced to 2 weeks and only requires 1 visit (Week -2; visit 2), i.e., the 2 screening visits will be merged. Similarly, if only a 2-week wash-out is required, screening visits 1 and 2 will be combined (Week -2; visit 2). All subjects will attend a screening visit 14 days before baseline (Week -2; visit 2). Eligibility will be assessed at the (first) screening visit and on Day 0 prior to randomisation.

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.

Treatment period (Week 0 to Week 16)

Following the screening period, approximately 200 subjects will be randomised 1:1 to one of the following groups stratified by disease severity (IGA of 3 or 4):

- Tralokinumab 600 mg (4 mL) at Day 0 (hereinafter “baseline”), then 300 mg (2 mL) Q2W.

- Placebo (4 mL) at baseline, then placebo (2 mL) Q2W.

Subjects will each receive 1 dose of Tdap and meningococcal vaccines given intramuscularly at Week 12.

The last administration of IMP will occur at Week 14.

Safety follow-up period (Week 16 to Week 30)
All subjects, except for those who transfer to the ECZTEND trial (LP0162-1337), will complete a full 14-week off-treatment follow-up period which includes 2 telephone contacts and an office visit at Week 30 for assessment of safety, PK, and ADA.

Long-term extension trial
Eligible subjects may be invited to enter an open-label, long-term extension trial conducted under a separate protocol (LP0162-1337, ECZTEND). Subjects who fulfil the eligibility criteria in the ECZTEND protocol can enter the trial at the Week 16 visit or up to 16 weeks after the last IMP injection in the present trial. Subjects who transfer to ECZTEND must have had their Week 16 visit under the current protocol (LP0162-1341).

7.2 Number of subjects needed

Assuming a screening failure rate of 25%, approximately 267 subjects will be screened and approximately 200 subjects will be randomly assigned to trial treatment. The statistical power considerations for this sample size (n=200) are described in Section 14.1.

This trial will be conducted at approximately 40 sites in the US and Canada. The anticipated minimum number of randomised subjects per trial site is 4 and the maximum number of subjects per trial site is 25.

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 30) or if they have transferred to the ECZTEND trial (Section 7.1).

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

Final collection of data for the primary endpoints will occur at Week 16.

7.4 Software

CDISC controlled terminology version 22-Dec-2017 was used for definition of controlled terminology used throughout this protocol and will be used for statistical programming and output. SDTM version 1.4 and SDTM implementation guide version 3.2 will be used for data tabulations.

8 Trial population

8.1 Subject eligibility

The investigator should only include subjects who meet all eligibility criteria, are not put at undue risk by participating in the trial, and can be expected to comply with the protocol. Hence, subjects are expected to complete wash-out of previous AD medications without experiencing intolerable worsening of AD symptoms during the screening period.

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

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

8.2 Inclusion criteria

For inclusion into this trial, subjects must fulfil all of the following 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 to 54 years, both included, at screening.
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 or for whom topical treatments are otherwise medically inadvisable (e.g., due to important side effects or safety risks).
    - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to higher potency (±TCI as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent TCS), whichever is shorter.

- Subjects with documented systemic treatment for AD in the past year are also considered as inadequate responders to topical treatments and are potentially eligible for treatment with tralokinumab after appropriate washout.
- Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the subject's treating physician.

6. AD involvement of ≥10% body surface area at screening and baseline (visit 3) 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. Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.
10. Women of childbearing potential must use a highly effective* form of birth control (confirmed by the investigator) throughout the trial and at least for 16 weeks (5 half-lives) after last administration of IMP.

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

8.3 Exclusion criteria

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

1. Concurrent enrolment in another clinical trial where the subject is receiving an IMP.
2. Previous randomisation in tralokinumab trials.
3. Subjects for whom administration of the meningococcal vaccine provided in this trial is contraindicated or medically inadvisable, according to local label of the vaccine.
4. Subjects for whom administration of the tetanus, diphtheria, and pertussis vaccine provided in this trial is contraindicated or medically inadvisable, according to local label of the vaccine.
5. Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis.
6. Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD.
7. 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.
8. Treatment with the following medications within 4 weeks prior to randomisation:
    - Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine, azathioprine, mycophenolate mofetil, Janus kinase inhibitors etc.).
    - Systemic corticosteroid use (excludes topical, inhaled, or intranasal delivery)
    - Three or more bleach baths during any week within the 4 weeks.
9. Treatment with the following medications within 2 weeks prior to randomisation
    - TCS.
    - TCI.
    - Topical PDE-4 inhibitor.

10. Receipt of any vaccine (except influenza virus vaccines) within 3 months prior to screening, any meningococcal vaccine within 1 year prior to screening, or any tetanus-, diphtheria-, or pertussis-containing vaccine within 5 years prior to screening, documented or subject-reported.
11. Receipt of any marketed (i.e. immunoglobulin, anti-IgE) or investigational biologic agent, including dupilumab:
    - Any cell-depleting agents including but not limited to rituximab: within 6 months prior to randomisation, or until lymphocyte count returns to normal, whichever is longer.
    - Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to randomisation.
12. Receipt of any investigational non-biologic agent within 5 half-lives prior to randomisation.
13. Receipt of blood products within 4 weeks prior to screening.
14. Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.
15. Known or suspected allergy or reaction to any component of the IMP formulations.
16. History of any active skin infection within 1 week prior to randomisation.
17. 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.
18. 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.
19. History of anaphylaxis following any biologic therapy.
20. History of immune complex disease.

21. 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.
22. Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care.
23. 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.
24. 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.
25. 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).
26. 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.
27. 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.

28. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.0 times the ULN (upper limit of normal) at screening.
29. 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.
30. 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.
31. Subjects who are legally institutionalised.
32. Pregnant, breastfeeding, or lactating women.
33. Employees of the trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.

8.4 Screening and screening failures

Subject identification number

Trial participation begins once written informed consent is obtained. Refer to Appendix 3B for details on the informed consent process. Once informed consent is obtained, a subject ID will be assigned by a central IRT system and the screening evaluations to assess eligibility criteria may begin. The subject ID will be used to identify the subject during the screening process and throughout trial participation, if applicable. Subjects who have given written informed consent to participate in the trial and who have been assigned a subject ID are considered 'screened' subjects.

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

Screening failures

Screening failures are defined as subjects who consent to participate in the trial but are not subsequently randomly assigned to trial treatment. A minimal set of screening failure information is required to ensure transparent reporting of screening failure subjects to meet

the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (22) and to respond to queries from regulatory authorities.

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

- Date of informed consent.
- Demographics (date of birth, sex, ethnicity, race).
- Reason for screen failure:
  - Failure to meet eligibility criteria.
  - Lost to follow-up.
  - Withdrawal by subject.
  - Other.
- Date of screen failure.
- Any AEs and SAEs.

In case of any SAEs, these must be followed-up as described in Section 13.7.

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 eCRF. Individuals who are re-screened will get a new subject ID.

9 Treatments

9.1 Description of IMP

9.1.1 Tralokinumab and placebo

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 syringe. Refer to Panel 4 for further details.

Panel 4: Identification of IMPs (tralokinumab and placebo)

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

The accessorised prefilled syringe is a single use, disposable system that is designed to administer the labelled dose of the system to the subcutaneous space during 1 injection and automatically provide a safety mechanism to reduce the occurrence of accidental needle sticks during disposal of the system.

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

9.1.2 Vaccines

The Tdap and menigococcal vaccines will be packaged in individually numbered kits, each containing 1 vial or 1 pre-filled syringe. Refer to Panel 5 for further details

Panel 5: Identification of IMPs (vaccines)

Investigational medicinal product	Dosage form and pack size	Active ingredient and concentration	Source
Tdap vaccine	Suspension for injection in 0.5 mL single-dose pre-filled syringes.	Combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine. The vaccine contains diphtheria toxoid, tetanus toxoid, and 3 purified pertussis antigens (pertussis toxoid, filamentous haemagglutinin, and pertactin) adsorbed onto aluminum salts. The final vaccine is formulated in saline. Each 0.5 mL dose is formulated to contain 5 limit of flocculation (Lf) of tetanus toxoid, 2.5 Lf of diphtheria toxoid, 8 mcg of inactivated pertussis toxoid, 8 mcg of filamentous haemagglutinin, and 2.5 mcg of pertactin (69 kDa outer membrane protein).	Commercially available; supplied by the CMO.
Meningococcal vaccine	Solution for injection in 0.5 mL single-dose vials.	Meningococcal (groups A, C, Y and W-135) polysaccharide diphtheria toxoid conjugate vaccine. Each 0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 mcg each of meningococcal A, C, Y and W-135 polysaccharides conjugated to approximately 48 mcg of diphtheria toxoid protein carrier.	Commercially available; supplied by the CMO.

9.2 Administration of IMP

9.2.1 Administration of tralokinumab and placebo

Dosing visits are shown in the schedule of trial procedures (Section 4). The last administration of IMP (tralokinumab/placebo) will occur at Week 14.

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

At subsequent visits (Q2W) in the 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 (2.0 mL).

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

IMP (tralokinumab/placebo) will be administered by a qualified, unblinded HCP (refer to Section 9.3.1 for blinding details). A minimum interval of 7 days is required between 2 dosing visits. IMP injections will be administered at the trial site when all assessments have been completed (Section 11.1).

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.

Although the suggested anatomical site for the tralokinumab/placebo injections at Week 12 is the right upper arm (refer to the injection rotation scheme described in the IMP manual), it should be noted that in this trial, the tralokinumab/placebo injections at Week 12 will be administered in one of the other allowed anatomical sites (anterior thigh or abdomen). This is due to the fact that the 2 vaccines administered at Week 12 must be injected intramuscularly in the deltoid area (Section 9.2.2).

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

After IMP administration
For the first 3 IMP dosing visits (Day 0, Week 2, and Week 4), subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 30 minutes with vital

signs taken at 30 minutes or until stable, whichever is later. Vital signs will be documented in the eCRF.

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

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

Conditions requiring IMP administration rescheduling
If any of the following should occur, the investigator should reschedule the visit and IMP should not be administered until the rescheduled visit:

- The subject has an intercurrent illness, that in the opinion of the investigator may compromise the safety of the subject in the trial (e.g., viral illnesses).
- The subject is febrile (defined as ≥38°C; ≥100.4°F) within 72 hours prior to IMP administration.

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

9.2.2 Administration of vaccines

At visit 9 (Week 12), subjects will each receive 1 dose of Tdap and meningococcal vaccines (refer to the schedule of trial procedures [Section 4]). The vaccines will be administered by trial staff on the same day the tralokinumab/placebo injections are administered; the vaccines will be given first, then tralokinumab/placebo will be given (see below).

The 2 vaccines will be given intramuscularly in the deltoid muscle of the upper arms, 1 vaccine in each arm. The injection site must be recorded in the source documents and recorded in the eCRF.

The subject will be kept under observation for 30 minutes following vaccination. After this observational period, the 2 tralokinumab/placebo injections will be given (Panel 7). Note that at Week 12, the tralokinumab/placebo injections will be given in the anterior thigh or abdomen.

Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc., and medical equipment to treat acute anaphylactic reactions must be immediately available at trial sites, and trial personnel should be trained to recognise and respond to anaphylaxis according to local guidelines.

Syncope can occur in association with administration of the vaccines. Procedures should be in place to prevent falling injury and to restore cerebral perfusion following syncope.

For each vaccine, the IRT will assign the required kit number for each subject.

Conditions requiring vaccine administration rescheduling
If any of the following should occur, the investigator should reschedule the visit and IMP (vaccines) should not be administered until the rescheduled visit:

- The subject has an intercurrent illness, that in the opinion of the investigator may compromise the safety of the subject in the trial (e.g., viral illnesses).
- The subject is febrile (defined as ≥38°C; ≥100.4°F) within 72 hours prior to IMP administration.

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

9.3 Treatment assignment

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

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

9.3.1 Blinding

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

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

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

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

Analysis of data per last subject's Week 16 visit
To support submission for marketing approval, an analysis of trial data up to and including visit 11 (Week 16) 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 16-week data. All staff involved in the conduct of the trial will remain blinded to treatment allocation for the entire duration of the trial. This principle will be applied to all investigator staff and to staff employed by the sponsor except for those who are directly involved in the execution of the analysis.

9.3.2 Emergency unblinding of individual subject treatment

While the safety of a subject always comes first, it is still important to carefully consider if unblinding is necessary to ensure a subject's safety. An emergency unblinding request can be

made by the investigators, HCPs who are not members of the trial staff, or authorised LEO personnel.

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

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

9.4 Background treatment (emollients)

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

9.5 Rescue treatment

If medically necessary (i.e., to control intolerable AD symptoms), rescue treatment for AD may be provided to trial subjects at the discretion of the investigator.

If possible, investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for subjects who do not respond adequately after at least 14 days of topical treatment.

Subjects who receive topical rescue treatment (TCS of any WHO class [see Appendix 8], or TCI) will continue treatment with IMP (tralokinumab/placebo) and will receive the vaccines. TCI may be used for rescue, but should be reserved for body areas where TCS is not advisable or on areas where continued treatment with TCS is considered unsafe.

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

be resumed if deemed appropriate by the investigator and sponsor's medical expert, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

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

9.6 Concomitant medication and concurrent procedures

Any medication or vaccine that the subject receives from 3 months prior to screening through safety follow-up (Week 30) must be recorded in the subject's medical record and the eCRF along with details such as:

- Medication name.
- Indication.
- Start and stop date of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose per administration, unit, and frequency.
- Route of administration.
- Dose form (cream, lotion, ointment, other); this is only required for topical treatments.

Similarly, concurrent procedures must also be recorded in the subject's medical record and the eCRF. The following data will be recorded: name of procedure, indication, body location (upper limb, lower limb, trunk, head), and start and stop date. Note: in this trial, only surgical procedures and procedures related to AD treatment (e.g., phototherapy or bleach baths) will be recorded.

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 9.7. The sponsor's medical expert should be contacted if there are any questions regarding concomitant or prior therapy.

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

The following concomitant medications related to AD treatment are permitted from screening through safety follow-up (Week 30):

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

9.7 Prohibited medication

The medications listed in Panel 6 are prohibited during the trial.

Panel 6: Prohibited medication

Medication	Prohibited from	Prohibited to	Temporary discontinuation of IMP required
Topical medications used for treatment of AD, including: • TCS of any WHO class. • TCI. • PDE-4 inhibitors.	Week -2 (2 weeks prior to randomisation)	Week 16 (end of treatment)	No
Use of UVA or UVB, psoralen + UVA (PUVA), other phototherapy, or tanning beds.	Week -6 (6 weeks prior to randomisation)	Week 16 (end of treatment)	No
Three or more bleach baths per week.	Week -4 (4 weeks prior to randomisation)	Week 16 (end of treatment)	No
Investigational agents other than tralokinumab.	3 months or 5 half-lives[1] prior to randomisation	Week 30 (safety follow-up)	Yes
Immunoglobulin.	3 months or 5 half-lives[1] prior to randomisation	Week 30 (safety follow-up)	Yes
Blood products.	4 weeks prior to screening	Week 30 (safety follow-up)	Yes
Systemic corticosteroids[2]	Week -4 (4 weeks prior to randomisation)	Week 30 (safety follow-up)	Yes
Systemic treatment for AD with an immunosuppressive or immunomodulating agent[3].	Week -4 (4 weeks prior to randomisation)	Week 30 (safety follow-up)	Yes
Allergen immunotherapy.	Randomisation	Week 30 (safety follow-up)	Yes
Vaccination of any kind (except influenza virus vaccines).	3 months prior to screening	Week 30 (safety follow-up)	Yes

1) Whichever is longer. For cell-depleting agents, the use is disallowed within 6 months of randomisation.
2) Note: nasal and inhaled corticosteroids are allowed.
3) Examples include cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, Janus kinase inhibitors, interferon-gamma, dupilumab, and other biologics.

AD, atopic dermatitis; IMP, investigational medicinal product; PDE-4, phosphodiesterase 4; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; UV, ultraviolet; WHO, World Health Organization.

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

Refer to Section 9.5 for principles for use of rescue treatment and re-initiation of IMP after discontinuation of prohibited systemic rescue treatment.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

Tralokinumab/placebo
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.

Vaccines
The IMP will be packaged in individually numbered kits, each containing 1 vial (meningococcal vaccine) or 1 pre-filled syringe (Tdap vaccine).

Primary and secondary packaging materials (vial/pre-filled 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.

Trial sites will be provided with local labels of the vaccines.

9.8.2 Storage of trial products

Tralokinumab/placebo and vaccines
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.

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

9.8.3 Drug accountability

Tralokinumab/placebo and vaccines
The investigator is fully responsible for the IMPs (tralokinumab/placebo and vaccines) at the trial site and for maintaining adequate control of the IMPs and for documenting all transactions with them.

An inventory must be kept of the IMP administered to each subject randomised in the trial. This inventory 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 be performed in the IRT.

The trial site will maintain trial kit cartons from used kits until reconciliation. The IMP must be fully accounted for by the CRA with the help of the unblinded HCP. 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. Prior to their return, the IMP must be fully accounted for by the CRA with the help of site staff responsible for dispensing the IMP. Accountability must be documented in the IRT.

Reporting in eCRF
The following data will be recorded in the eCRF for tralokinumab/placebo:

- Date and time of IMP administration.
- Site of IMP injection (upper arm, anterior thigh, or abdomen).

- IMP kit numbers.

The following data will be recorded in the eCRF for the vaccines:

- Date and time of IMP administration.
- Site of IMP injection (left upper arm, right upper arm, other site [will require a comment]).
- IMP kit numbers.

9.8.4 Treatment compliance

All IMP injections (tralokinumab/placebo and vaccines) will be performed by site staff who will also keep the accountability records up to date. Any non-compliance (subject received partial dose; subject received no dose) and the reason for the non-compliace will be recorded in the eCRF.

9.8.5 Trial product destruction

Used pre-filled syringes (tralokinumab/placebo, Tdap vaccine) and meningococcal vaccine vials will be destroyed at the trial site provided the trial site has procedures in place for such IMP destruction; this requires that the trial site is able to issue a certificate of destruction. Trial sites which do not have such IMP destruction procedures in place will dispose used pre-filled syringes (tralokinumab/placebo, Tdap vaccine) in sharps bins which will be shipped to the CMO at the end of the trial together with used vaccine vials.

Unused IMP (tralokinumab/placebo and vaccines), used pre-filled syringes, and used vaccine vials returned to the CMO will be destroyed by the CMO according to approved procedures and/or local requirements.

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.

9.10 Reporting product complaints

Any defects or issues with the IMP (tralokinumab/placebo/vaccines) as well as any device deficiency (including malfunctions, use errors, and inadequate labelling) must be reported to

Global Pharmacovigilance, LEO on the trial specific (paper) Complaint Form within 3 days of first knowledge.

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

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

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

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

Global Pharmacovigilance, LEO contact information for reporting product complaints:

Fax number: +45 7226 3287

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

10 Discontinuation and withdrawal

10.1 General principles

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

Discontinued subjects will not be replaced.

10.2 IMP discontinuation rules

10.2.1 Reasons for permanent discontinuation of IMP

Subjects will be permanently discontinued from IMP in the event of:

- Anaphylactic reaction or other severe systemic reaction to IMP injection.
- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.
- Diagnosis of a malignancy during the trial, excluding carcinoma in situ of the cervix, or localised squamous or basal cell carcinoma of the skin.
- Evidence of pregnancy.
- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status.
- Severe laboratory abnormalities:
    - ALT and/or AST values >3x ULN with total bilirubin >2x ULN (unless elevated bilirubin is related to Gilbert-Meulengracht Syndrome).
    - Confirmed AST and/or ALT >5x ULN (for more than 2 weeks).

Refer to Section 10.3 for details on the handling of subject discontinuation and to Panel 2 for assessments to be performed at an early termination visit for subjects who discontinue IMP permanently.

10.2.2 Reasons for temporary discontinuation of IMP

IMP dosing may be temporarily suspended in the event of:

- Other intercurrent illnesses or major surgery.
- An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents.
- Treatment with some of the prohibited medications given in Panel 6 (medications requiring temporary discontinuation of IMP are highlighted in the column 'Temporary discontinuation of IMP required').

IMP dosing may resume after the medication leading to suspension of IMP is discontinued. Refer to Section 9.5 for details regarding re-initiation of IMP after discontinuation of systemic rescue treatment.

10.3 Early termination assessments

Permanent discontinuation of IMP

Subjects who permanently discontinue IMP for any reason will be asked to attend an early termination visit and return to the trial site for 2 additional visits as indicated below (see the schedule of trial procedures [Section 4] for data to be collected at these 3 visits). The investigator will review any AEs which will be followed up according to Section 13.7, if the subject agrees.

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

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

Refer to Section 11.10 for details on data to be recorded in the eCRF for subjects who permanently discontinue IMP.

Withdrawal from trial

Subjects who withdraw from the trial for any reason should attend an early termination visit as soon as possible after last administration of IMP (see the schedule of trial procedures [Section 4] for data to be collected at an early termination visit). The investigator will review any AEs which will be followed-up according to Section 13.7, if the subject agrees.

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

Refer to Section 11.10 for details on data to be recorded in the eCRF for subjects who withdraw from the trial.

10.4 Lost to follow-up

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

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

- The trial site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to 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.

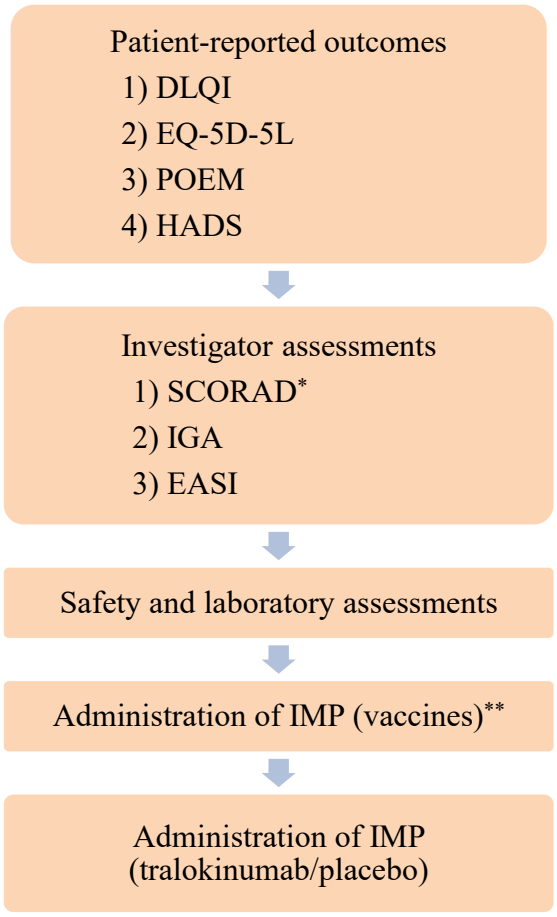
11 Trial assessments and procedures

11.1 Overview

During this trial, subjects will attend a total of 11 or 12 scheduled visits at the trial site. The visits and procedures to be carried out at each visit are summarised in the schedule of trial procedures (Panel 2). Refer to Section 7.1 for further details on the trial design.

Assessments and procedures at each trial visit should be performed in the order shown in Panel 7.

Panel 7: Sequence of assessments and procedures



*First component C, then component A and B; ***Week 12 only.

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D-5L, EuroQoL 5-Dimension Health Questionnaire 5-Level; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; IMP, investigational medicinal product; POEM, Patient Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis.

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

The investigators performing the assessments must not be involved in the administration of IMP (tralokinumab/placebo). See Section 9.3.1 for further details.

To reduce inter-rater variability, the same investigator should perform all the evaluations for a given subject throughout the entire trial period, if possible.

During the course of the trial, subjects may need to be seen at unscheduled visits. The assessments to be performed at an unscheduled visit are left to the investigator's discretion (could include any assessment performed at an early termination visit). Refer to the schedule of trial procedures (Panel 2) for assessments to be considered at an unscheduled visit.

11.2 Assessments performed only at screening/baseline

11.2.1 Demographics

The following demographic data will be recorded:

- Age: date, month and year of birth. Where it is not allowed to collect the subject's full date of birth, only month and/or year of birth will be collected as per local legislation. In these cases, the subject's age in years will also be recorded.
- Sex: female, male.
- 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.

11.2.2 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.

For each condition, diagnosis, or surgical procedure, the start date and stop date will be recorded; it will also be recorded if the condition, diagnosis, or surgical procedure is ongoing.

11.2.3 Height and weight

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

11.2.4 Body surface area involvement

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

11.2.5 Columbia-Suicide Severity Rating Scale

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

criterion no. 25 does not apply. Further details on the assessment according to the C-SSRS are included in the efficacy assessment & C-SSRS manual.

11.3 Efficacy assessments

11.3.1 Investigator's Global Assessment

The IGA is an instrument used in clinical trials to rate the severity of the subject's global AD and is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Panel 8). The IGA score will be assessed according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. The IGA is included in the efficacy assessment & C-SSRS manual.

Panel 8: Investigator's Global Assessment

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

11.3.2 Eczema Area and Severity Index

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (26). The EASI score will be assessed according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit.

The EASI is a composite index with scores ranging from 0 to 72, with higher values indicating more severe or more extensive condition. The index will be calculated as shown in Panel 9. Briefly, the investigator will assess the severity of 4 AD disease characteristics (erythema, induration/papulation, excoriation, and lichenification) on the 4 body regions (head/neck, trunk, upper extremities, lower extremities); severity will be assessed according to the scale shown in Panel 10. For each body region, a severity sum score will be calculated which will be multiplied by an area score (Panel 10) and by a weighting factor. The EASI score equals the sum of the scores obtained for each body region (Panel 9). Refer to the efficacy assessment & C-SSRS manual for further details on these assessments.

Panel 9: Calculation of the Eczema Area and Severity Index

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

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

Panel 10: EASI severity score scale and area score scale

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

Note: half-steps (0.5, 1.5, 2.5) are allowed.

Area score scale	
0	0% affected area
1	1% to 9% affected area
2	10% to 29% affected area
3	30% to 49% affected area
4	50% to 69% affected area
5	70% to 89% affected area
6	90% to 100% affected area

EASI, Eczema Area and Severity Index.

11.3.3 Scoring Atopic Dermatitis

The SCORAD is a validated tool to evaluate the extent and severity of AD lesions, along with subjective symptoms (28). The maximum total score is 103, with higher values indicating more severe disease. SCORAD will be assessed according to the schedule of trial procedures (Section 4). Refer to the efficacy assessment & C-SSRS manual for further details on these assessments.

The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit.

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

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

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

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

Note: dryness is evaluated on uninvolved areas.

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

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

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

11.3.4 Patient-reported outcomes

11.3.4.1 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 (29). 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 according to the schedule of trial procedures in Section 4. It will be completed electronically on the device supplied to the trial site and is included in the investigator trial file.

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

11.3.4.3 Patient-Oriented Eczema Measure

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

Section 4. It will be completed electronically on the device supplied to the trial site and is included in the investigator trial file.

11.3.4.4 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 (32). The tool consists of 14 items that assess the subject's anxiety (7 items) and depression (7 items) during the last week. Each question is scored from 0 to 3, with high scores indicating a poor state. The HADS will be completed electronically on the device supplied to the trial site according to the schedule of trial procedures (Section 4) and is included in the investigator trial file.

11.4 Safety assessments

11.4.1 Vital signs

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

If an abnormal vital sign at screening is considered to be clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be randomised into the trial (respecting exclusion criterion no. 27).

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

Reporting in eCRF
Vital signs and the date and time they were measured will be recorded in the eCRF. 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 13.3. 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 13.3.

11.4.2 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 trial procedures (Section 4).

If an unacceptable abnormal finding is identified during the physical examination at the screening visit, the subject must not be randomised into the clinical trial (respecting exclusion criterion no. 27)

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

Clinically significant abnormal physical examination findings at the (first) screening visit will be documented as medical history in the eCRF. If an abnormal physical examination 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 13.3. 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 13.3.

11.4.3 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 trial 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. 27); if such a subject is enrolled, the investigator will provide a justification in the medical record.

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

Reporting in eCRF
It will be recorded in the eCRF if an ECG was performed and, if applicable, the investigator's assessment of ECG results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant'). If an ECG was not performed, a reason should be given.

Clinically significant abnormal ECG findings at the (first) screening visit will be documented as medical history in the eCRF. If an abnormal ECG at any other visit than the first screening visit is considered by the investigator to be clinically significant, it will be reported as an AE in accordance with Section 13.3. 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 13.3.

11.4.4 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 trial 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 trial procedures in Section 4. The visit date and the outcome of the urine pregnancy test will be recorded in the eCRF ('positive', 'negative').

Note that pregnant subjects must discontinue IMP immediately (Section 10.2.1).

11.4.5 Laboratory testing

Samples for laboratory testing will be collected according to the schedule of trial procedures (Section 4).

The following safety samples will be analysed by a central laboratory: chemistry, haematology, serology, and serum pregnancy (Panel 11).

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, destruction, and shipment of samples, as well as laboratory contact information specific to this trial.

Panel 11: Clinical laboratory tests

Chemistry	Haematology
Sodium Potassium Creatinine Urea nitrogen Calcium Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Gamma glutamyl transferase Bilirubin[1] Lactate dehydrogenase Cholesterol LDL cholesterol HDL cholesterol Triglycerides Glucose (non-fasting) Albumin Protein Tryptase[2]	Erythrocytes Hematocrit Hemoglobin Erythrocyte mean corpuscular volume Erythrocyte mean corpuscular haemoglobin concentration Leukocytes Neutrophils Neutrophils/leukocytes Lymphocytes Lymphocytes/leukocytes Monocytes Monocytes/leukocytes Eosinophils Eosinophils/leukocytes Basophils Basophils/leukocytes Thrombocytes
	Serology
	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[4,6]**
Protein Glucose Ketones Occult blood Leukocytes Nitrite	Choriogonadotropin beta

1) If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
2) Only measured in case of suspected anaphylaxis (Section 9.2.1).
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.
6) Only female subjects of child-bearing potential.

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

The investigator must evaluate all results outside the reference range ('clinically significant' or 'not clinically significant') and sign and date. The signed and dated version will be filed with the investigator's trial documentation. Clinically significant abnormal tests at baseline (Week 0) or later must be repeated to confirm the abnormality.

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. 27, 28, and 29).

Reporting in eCRF
At each visit, the site staff will record the following in the eCRF: Date and time of blood sample (or that a blood sample was not taken) and the investigator's assessment of the results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant'). In addition, the site staff will record in the eCRF if a urine sample was taken and the investigator's assessment of the result ('normal', 'abnormal').

Clinically significant abnormal laboratory findings at the (first) screening visit will be documented as medical history in the eCRF. If an abnormal laboratory 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 13.3. 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 13.3.

11.4.6 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 trial procedures (Section 4).

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

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.

11.5 Assessment of vaccine responses

Blood samples for assessment of vaccine-specific serum antibody responses will be collected at the time points specified in the schedule of trial procedures (Section 4).

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

The antibody response to Tdap vaccine will be assessed by measuring serum anti-tetanus IgG by an immunoassay. The antibody response to meningococcal vaccine will be assessed by measuring serum anti-meningococcal IgG by an immunoassay.

Reports of serum antibody responses will be provided by the laboratory to the trial sites at the end of the trial. The investigator must sign and date these reports.

Reporting in eCRF
It will be recorded in the eCRF if the blood samples to assess vaccine response were taken; if not, a reason will be provided.

11.6 Pharmacokinetic assessments

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

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

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

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

11.7 Pharmacodynamics and pharmacogenomics

Not applicable.

11.8 Other assessments

Not applicable.

11.9 Estimate of total blood volume collected

Blood samples will be drawn for chemistry, haematology, serology, PK, ADA, and vaccine-specific serum antibody responses. The total volume of blood to be drawn is approximately 150 mL which is less than the volume of blood drawn during a blood donation (approximately 500 mL).

11.10 End of trial

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

End-of-treatment form
An end-of-treatment form will be completed when the subject has had their last administration of IMP. The following data will be recorded on this form:

- Date of last administration of IMP (tralokinumab/placebo).
- Has the subject completed the treatment period (yes/no). If no, the primary reason for permanent discontinuation of IMP must be recorded (lack of efficacy, AE, withdrawal by subject, lost to follow-up, death, other).

The primary reason for permanent discontinuation of IMP must also be recorded in the medical records.

End-of-trial form
An end-of-trial form will be completed when the subject has had their last visit. The following data will be collected:

- Did the subject complete the trial (yes/no).
- Has the subject been transferred to LP0162-1337 (yes/no). If yes, the site will record the last visit the subject attended, including phone calls (Week 16, Week 20, Week 24, Week 30, unscheduled visit).
- Did the subject attend the nominal Week 16 visit (yes/no). If no, the primary reason for not attending the visit must be recorded (lack of efficacy, AE, withdrawal by subject, lost to follow-up, death, other).

- Did the subject attend the safety follow-up visit (yes/no). If no, the primary reason for not attending the visit must be recorded (lack of efficacy, AE, withdrawal by subject, lost to follow-up, death, transferred to LP0162-1337, other).
- Date of last contact.
- Primary reason for withdrawal from trial (lack of efficacy, adverse event, withdrawal by subject, lost to follow-up, death, other).

11.11 Storage of biological samples

The samples analysed by the central laboratory (Panel 11) will be destroyed after analysis.

PK samples will be retained for as long as the quality of the material permits evaluation but for no longer than 12 months after completion of the CTR.

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

Samples collected to assess the vaccine-specific antibody response will be retained for as long as the quality of the material permits evaluation but for no longer than 12 months after completion of the CTR.

12 Scientific rationale for trial design and appropriateness of assessments

This trial will assess immunisation responses against 2 different vaccines (a combined diphtheria, tetanus, and acellular pertussis vaccine and a meningococcal vaccine) in adults with moderate-to-severe AD who are treated with tralokinumab, to ensure a broad assessment of immune competence in subjects treated with tralokinumab.

Since concomitant administration of vaccines may affect the efficacy of tralokinumab in patients with AD, a placebo-controlled parallel group design has been chosen to evaluate the efficacy and safety of Q2W tralokinumab concomitantly administered with vaccines in the target patient population.

The vaccines will be given after 12 weeks of tralokinumab/placebo treatment to ensure that the trial drug effect has reached near-steady state levels when the vaccines are administered.

The vaccine responses will be analysed at Week 16 when the tralokinumab/placebo treatment schedule is complete. This allows an evaluation of the vaccine responses 4 weeks after vaccination which is the time span used to evaluate efficacy of these vaccine products (33, 34).

The trial will evaluate the percentage of subjects achieving a positive anti-tetanus response at Week 16 (defined as a 3-fold IgG increase compared to Week 12 if IgG ≤1.0 IU/mL at Week 12; or IgG ≥2.5 IU/mL if IgG >1.0 IU/mL at Week 12) and a positive anti-meningococcal response at Week 16 (defined as IgG ≥3.0 mcg/mL with at least a 3-fold increase compared to Week 12). These response criteria were developed based on the criteria for positive vaccine response in the assays used for determining anti-tetanus and anti-meningococcal IgG concentrations. The anti-tetanus response definition takes into account that some subjects may have high pre-vaccination anti-tetanus IgG levels and may therefore not be able to elicit the same increase in anti-tetanus IgG levels as those with low pre-vaccination levels.

The results should be generalisable to an adult population with AD. The age limit of 54 years is chosen to ensure that no subjects older than the meningococcal vaccine age limit of 55 years are included.

Subjects who do not achieve or lose clinical response will not be excluded from further participation in the trial. This approach has been chosen to increase the likelihood that subjects from the placebo arm will stay in the trial until administration of the vaccines (Week 12) and evaluation of the vaccine responses (Week 16). Subjects who complete the

Week 16 visit may be invited for the open-label, long-term extension trial conducted under a separate clinical trial protocol (ECZTEND).

The clinical efficacy of tralokinumab treatment will be assessed by IGA, EASI, and SCORAD. IGA is a key instrument used in clinical trials to rate the severity of the subject's global AD. EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (26). SCORAD is a validated tool to assess the extent and severity of AD lesions and subjective symptoms (28).

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

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

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

13 Adverse events

13.1 Definition and classification of adverse events

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

Classification of AEs in terms of severity, causality and outcome is defined in Appendix 2. A causality assessment will be made for both tralokinumab/placebo and each of the vaccines.

13.2 Collection of adverse event reports

AEs must be collected from time of first trial-related activity after the subject has signed the informed consent form (ICF) until completion of the clinical trial (defined as per Section 7.3).

AEs must be assessed by medically qualified personnel.

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

Refer to Sections 11.4.1 to 11.4.5 for principles for data entry in the eCRF.

13.3 Reporting of adverse events

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

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

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

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

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

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

13.4 Reporting of serious adverse events

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

13.4.1 Investigator reporting responsibilities

Any SAE must be reported to LEO on the (paper) SAE Form within 24 hours of first knowledge. This report should contain an assessment of available information on seriousness, severity, causal relationship to the IMP (tralokinumab/placebo), IMP (vaccines), IMP device, 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 at LEO using the e-mail address or fax number below:

Global Pharmacovigilance at LEO

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

Fax number: +45 7226 3287

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

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

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

SAEs occurring after the completion of the clinical trial (defined as per Section 7.3) should not be routinely sought or collected. However, such events should be reported to Global

Pharmacovigilance at LEO (see contact details above) if the investigator becomes aware of them.

13.4.2 LEO reporting responsibilities

Global Pharmacovigilance at LEO is responsible for assessing whether or not an SAE is expected. The relevant reference safety information documents for this clinical trial are:

- For the IMP (tralokinumab/placebo), the Investigator's Brochure, edition 17 and subsequent updates must be used.
- For the IMP (Tdap and meningococcal vaccines), the latest version of the approved labelling in the US must be used.

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

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

For all countries except the US, the following reporting requirements apply: 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) according to the current applicable legislation in the concerned countries. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

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

13.5 Other events that require expedited reporting

13.5.1 Pregnancy

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

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

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

13.6 Reporting of other events

13.6.1 Adverse events of special interest

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

Panel 12: Adverse events of special interest

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

13.6.2 Overdose

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

The term ‘overdose’ must be recorded on the AE form of the eCRF. In addition, AEs originating from overdose must be recorded as separate events. If an AE originating from an overdose qualifies as an SAE, expedited reporting is required (Section 13.4).

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

13.6.3 Medication error

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

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

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

13.6.4 Misuse

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

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

13.6.5 Abuse

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

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

13.6.6 Aggravation of condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s), compared to screening, must be reported as an AE in accordance with Section 13.3. If the AE originating from aggravation of condition qualifies as an SAE, expedited reporting is required (Section 13.4).

13.7 Follow-up for final outcome of adverse events

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

13.8 Handling of an urgent safety measure

An urgent safety measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined as *“…the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard.*” (35).

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

The investigator must immediately inform LEO – by contacting the clinical project manager or medical expert – of this change in the clinical trial procedure or of the temporary halt

providing full details of the information and the decision making process leading to the implementation of the urgent safety measure.

LEO must act immediately upon receipt of the urgent safety measure notification in accordance with internal procedures and local legislation.

14 Statistical methods

14.1 Sample size

A total of 200 subjects will be randomised 1:1 to tralokinumab or placebo to ensure that a sufficient number of subjects complete the trial and fulfil the definition of the per protocol set which is considered the primary analysis set for establishing non-inferiority between tralokinumab and placebo with regard to immune responses to vaccines.

With 200 subjects in the FAS and 160 subjects anticipated in the per protocol set, the trial will provide 98% power to establish non-inferiority with regard to positive anti-tetanus response based on a one-sided significance level of 2.5%, assuming a response rate of 80% in both arms and a non-inferiority margin of -25%. Assuming a positive anti-meningococcal response rate of 80% in both arms, an IGA 0/1 response rate of 30% (tralokinumab) versus 10% (placebo), and an EASI75 response rate of 40% (tralokinumab) versus 15% (placebo), the trial will provide approximately 89% power for rejecting all 4 hypotheses related to the primary and secondary endpoints with each hypothesis tested at a one-sided 2.5% significance level. This evaluation is assuming no correlation between the primary and secondary endpoints.

To our knowledge there is no established margin in the literature for showing non-inferiority with regard to immune responses to vaccines and the sample size of previously conducted trials with similar objective varies. In a similar type of trial with dupilumab versus placebo in adults with moderate-to-severe atopic dermatitis (36), a total of 194 subjects was randomised (1:1) to assess vaccine response but no non-inferiority margin was pre-specified. By contrast, in a trial with ixekizumab versus placebo in healthy subjects, a total of 84 subjects were randomised (1:1) and a non-inferiority margin of -40% was pre-specified (ClinicalTrials.gov NCT02543918). Similarly, a non-inferiority margin of -40% was pre-specified in a trial with secukinumab versus placebo in healthy subjects (37).

On the basis of knowledge from previous trials, the proposed sample size and non-inferiority margin of -25% is considered appropriate to assess the primary objective of the trial.

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All subjects randomised to treatment are included in the FAS and will be analysed for efficacy up to Week 16. Exclusions from the FAS can be considered in special cases as described in

ICH E9, Section 5.2.1, Full Analysis Set. If it is decided to exclude a randomised subject from the FAS, a justification addressing ICH E9 will be given.

A per protocol analysis set will be defined by excluding subjects from the FAS for whom any of the following conditions apply:

- Receive no treatment with the IMP (vaccines).
- Provide no vaccine data at Week 16.
- Are known to have taken the wrong IMP throughout the treatment period.
- Do not fulfil the inclusion criteria no. 3, 6, 7, 8.
- Meet exclusion criterion related to receipt of other vaccines (that is, exclusion criterion no. 10).
- Initiate systemic rescue treatment prior to Week 10 and who are still treated with or exposed to systemic rescue treatment at Week 10 (that is, Week 10 [visit 8] occurs within 5 half-lives after the last dose of systemic rescue medication).
- Initiate systemic rescue treatment at Week 10 or later.
- Have missed more than 2 doses of tralokinumab/placebo before vaccine administration.
- Have missed any of the last 2 doses of tralokinumab/placebo before vaccine administration (that is, Weeks 8 and 10).

The per protocol analysis set will be used as primary analysis set for the vaccine antibody responses at Week 16 (primary endpoints; Panel 13). For the secondary endpoints (IGA 0/1 and EASI75 at Week 16), the FAS analysis will be considered primary.

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

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

14.3 Statistical analysis

14.3.1 Disposition of subjects

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

14.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects and the per protocol analysis set. The presentations will be overall and by treatment group. Presentations of age, sex, ethnicity, and race will also be given by baseline disease severity (IGA 3 or 4).

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

14.3.3 Exposure and treatment compliance

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

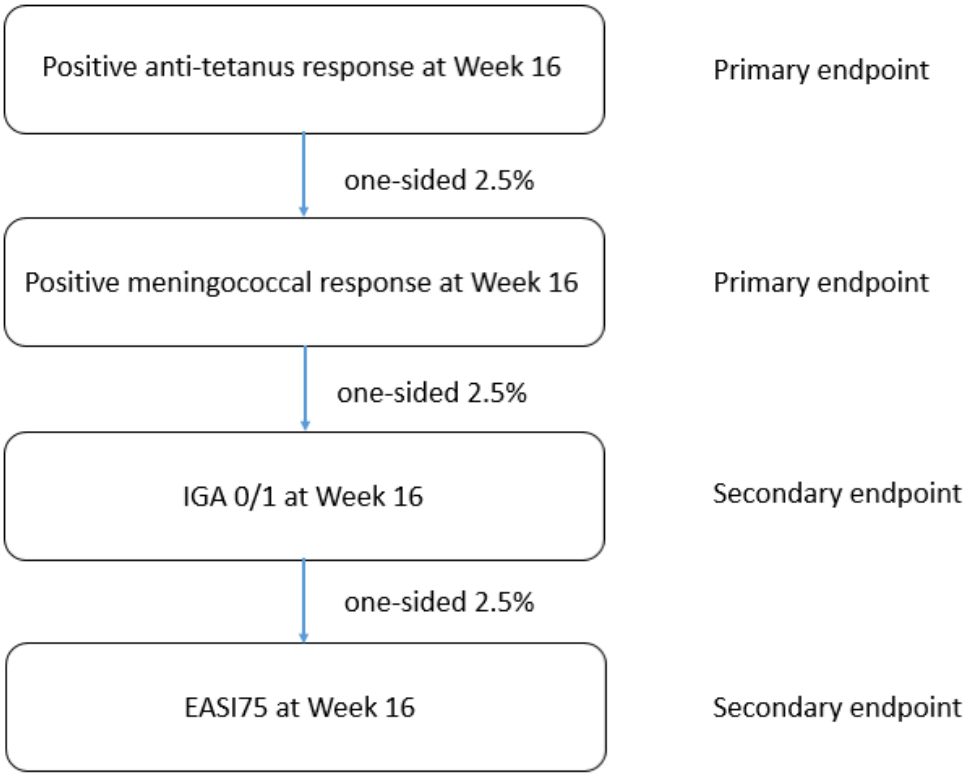
Adherence to treatment regimen will be recorded in the eCRF. If any complications or deviations in administration are observed, these will be described as protocol deviations. Adherence will be presented for the safety analysis set for each treatment group.

14.3.4 Multiple testing procedure

The primary and secondary endpoints will be evaluated hierarchically in the order shown in Panel 13.

The hypothesis relating to a specific endpoint cannot be rejected unless all hypotheses relating to endpoints earlier in the hierarchy are also rejected.

Panel 13: Testing procedure for primary and secondary endpoints



EASI, Eczema Area and Severity Index; EASI75, at least 75% reduction in EASI score; IGA, Investigator's Global Assessment.

Non-inferiority hypothesis to be tested for the primary endpoints: H_0: $\pi_{tralo}-\pi_{placebo} \leq -25\%$ versus H_1:$\pi_{tralo} -\pi_{placebo} > -25\%$,

Superiority hypothesis to be tested for the secondary endpoints: H_0: $\pi_{tralo}-\pi_{placebo} \leq 0\%$ versus H_1:$\pi_{tralo} -\pi_{placebo} > 0\%$,

where π_{tralo} and $\pi_{placebo}$ denotes the response rate with tralokinumab and placebo, respectively.

All hypotheses will be tested at a one-sided 2.5% significance level. For the non-inferiority hypotheses, the null hypothesis will be rejected if the two-sided 95% CI for the difference in immune response rate lies entirely to the right of the non-inferiority limit (-25%). For the superiority hypotheses, a two-sided 95% CI for the difference in response rates and a corresponding two-sided p-value will be calculated; the null hypothesis will be rejected if the p-value is smaller than 5% and the point estimate is in favour of the alternative hypothesis (that is, greater than 0).

14.3.5 Analysis of primary endpoints

Positive anti-tetanus response at Week 16 (3-fold IgG increase compared to Week 12 if IgG ≤1.0 IU/mL at Week 12; or IgG ≥2.5 IU/mL if IgG >1.0 IU/mL at Week 12) and positive anti-meningococcal response at Week 16 (IgG ≥3.0 mcg/mL with at least a 3-fold increase compared to Week 12) are binary endpoints. The difference in response rates between treatment groups will be calculated using the Mantel-Haenszel estimate of the risk difference stratified by baseline disease severity (IGA 3 or 4) together with the 95% CI. Non-inferiority of tralokinumab will be demonstrated if the lower limit of the 95% CI is greater than -25%.

The primary endpoints will be analysed for FAS and the per protocol set; the per protocol analysis will be considered the primary analysis. Analyses will be based on observed data; hence, missing data will not be imputed.

14.3.6 Analysis of secondary endpoints

14.3.6.1 Overview of estimand framework

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 2 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 10.3. 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 FAS unless otherwise specified.

14.3.6.2 Primary estimand: 'composite'

The primary estimand for the first 2 secondary endpoints will be:

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

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

Primary analysis for the primary estimand

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

The difference in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test stratified by baseline disease severity (IGA 3 or 4). The treatment estimate and the corresponding 95% CI will be presented. The null hypothesis of no difference in response rates between tralokinumab and placebo will be tested against the 2-sided alternative that there is a difference.

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 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 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.

14.3.6.3 Secondary estimand: 'hypothetical'

The secondary estimand for the first 2 secondary endpoints will be:

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

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

Primary analysis of the secondary estimand

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

IGA 0/1 responder imputation

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

1. In each group, intermittent missing values will be imputed using LOCF to obtain a monotone missing data pattern.
2. An ordinal logistic regression model assuming proportional odds will be fitted to the IGA value at Week 2. The model will include baseline disease severity (IGA 3 or 4) as factor. 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=13827641).

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 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 2 preceding visits will be included as factors in addition to 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 2 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=45624941).
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 baseline disease severity (IGA 3 or 4) as a factor. 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=11109941).
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 baseline disease severity (IGA 3 or 4) as a factor together with the EASI value at Week 2 as covariate. The estimated parameters, and their variances, will be used to impute missing values at Week 4.
4. This stepwise procedure will then be repeated sequentially for Week 6, 8, 10, 12, 14, and 16 with the modification that only the EASI values from the preceding 2 visits will be included as covariates in addition to baseline EASI as a covariate and baseline disease severity as a factor. 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 baseline disease severity (IGA 3 or 4). The estimates and standard errors from the 100 analyses will be pooled to one estimated treatment difference and associated standard error using Rubin's rule to draw inference. From these pooled estimates, the 95% CI for the treatment difference will be calculated.

Sensitivity analysis for the secondary estimand

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

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

14.3.6.4 Tertiary estimand: 'treatment policy'

The tertiary estimand for the first 2 secondary endpoints will be:

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

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

Primary analysis for the tertiary estimand

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

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

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

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

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

14.3.7 Analysis of other endpoints

To support the secondary endpoints, EASI50 at Week 16, EASI90 at Week 16, SCORAD75 at Week 16, and SCORAD50 at Week 16 will be analysed and presented for the FAS. These 4 endpoints will be analysed as described for the primary analysis of the primary estimand for the secondary efficacy endpoints.

The change from baseline to Week 16 in EASI, SCORAD, DLQI, EQ-5D-5L, POEM, and HADS 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

$$= \text{treatment} \times \text{visit} + \text{baseline SCORAD} \times \text{visit} + \text{baseline IGA}$$

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. Data collected after permanent discontinuation of IMP or after initiation of rescue medication will not be included in the analysis. All analyses will be based on the FAS.

14.3.8 Analysis of safety

The analyses of safety will be based on the safety analysis sets.

14.3.8.1 Adverse events

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

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

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

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

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

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

14.3.8.2 Vital signs

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

14.3.8.3 Clinical laboratory evaluation

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

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

14.3.8.4 Pharmacokinetics

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

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

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

14.3.8.5 Anti-drug antibodies

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

The association of ADA status across the trial (positive versus negative) with AEs/SAEs may be evaluated. In addition, the association of ADA titres (≥ median titre in positive subjects versus < median titre) with AE/SAEs may be evaluated for ADA-positive treated subjects only. The ADA-positive subjects across the trial may also be divided into persistent positive versus transient positive. A subject will be considered as persistent positive if he/she has positive ADA for at least 2 consecutive visits with ADA assessment. Otherwise, the subject will be considered as transient ADA positive. The associations between ADA and AE/SAEs may be summarised for both persistent positive subjects versus transient positives subjects.

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

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

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

14.3.9 Interim analysis

No interim analysis is planned.

14.3.10 General principles

All hypotheses will be tested at a one-sided 2.5% significance level. This will be done by calculating the two-sided 95% CIs and p-value (note that for the non-inferiority hypotheses a different approach will be used).

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.

14.3.11 Handling of missing values

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

15 References

1. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol. 2013;132(5):1132-1138.
2. Hanifin JM, Reed ML, Eczema Prevalence and Impact Working Group. A population based survey of eczema prevalence in the United States. Dermatitis. 2007;18(2):82-91.
3. Bieber T. Atopic dermatitis. N Engl J Med. 2008;358(14):1483-1494.
4. Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016;387(10023)1109-1122.
5. Kiebert G, Sorensen SV, Revicki D, Fagan SC, Doyle JJ, Cohen J, et al. Atopic dermatitis is associated with a decrement in health-related quality of life. Int J Dermatol. 2002;41(3):151-158.
6. Tazawa T, Sugiura H, Sugiura Y, Uehara M. Relative importance of IL-4 and IL-13 in lesional skin of atopic dermatitis. Arch Dermatol Res. 2004;295(11):459-464.
7. Omori-Miyake M, Yamashita M, Tsunemi Y, Kawashima M, Yagi J. In vitro assessment of IL-4- or IL-13-mediated changes in the structural components of keratinocytes in mice and humans. J Invest Dermatol. 2014;134(5):1342-1350.
8. Aleksza M, Lukács A, Antal-Szalmás P, Hunyadi J, Szegedi A. Increased frequency of intracellular interleukin (IL)-13 and IL-10, but not IL-4, expressing CD4+ and CD8+ peripheral T cells of patients with atopic dermatitis. Br J Dermatol. 2002;147(6):1135-1141.
9. Purwar R, Werfel T, Wittmann M. IL-13-stimulated human keratinocytes preferentially attract CD4+CCR4+ T cells: possible role in atopic dermatitis. J Invest Dermatol. 2006;126(5):1043-1051.
10. Oh MH, Oh SY, Lu J, Lou H, Myers AC, Zhu Z, Zheng T. TRPAA1-dependent pruritus in IL-13-induced chronic atopic dermatitis. J Immunol. 2013;191(11):5371-5382.
11. Zheng T, Oh MH, Oh SY, Schroeder JT, Glick AB, Zhu Z. Transgenic expression of interleukin-13 in the skin induces a pruritic dermatitis and skin remodeling. J Invest Dermatol. 2009;129:742-751.
12. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016 Dec 15;375(24):2335-2348.

13. May RD, Monk PD, Cohen ES, Manuel D, Dempsey F, Davis NH, et al. Preclinical development of CAT-354, an IL-13 neutralizing antibody, for the treatment of severe uncontrolled asthma. Br J Pharmacol. 2012;166(1):177-193.

14. Thom G, Minter R. Optimization of CAT-354, a therapeutic antibody directed against interleukin-13, using ribosome display. Methods Mol Biol. 2012;805:393-401.

15. Blanchard C, Mishra A, Saito-Akei H, Monk P, Anderson I, Rothenberg ME. Inhibition of human interleukin-13-induced respiratory and oesophageal inflammation by anti-human interleukin-13 antibody (CAT-354). Clin Exp Allergy. 2005;35(8):1096-1103.

16. Hershey GK. IL-13 receptors and signaling pathways: an evolving web. J Allergy Clin Immunol. 2003;111(4):677-690.

17. Nomura I, Goleva E, Howell MD, Hamid QA, Ong PY, Hall CF, et al. Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. J Immunol. 2003;171(6):3262-3269.

18. Looney RJ, Diamond B, Holers VM, Levesque M, Moreland L, Nahm M, et al. Guidelines for assessing immunocompetency in clinical trials for autoimmune diseases. Clin Immunol. 2007;123(3):235-243.

19. Moffat GJ, Davies R, Kwon G, Retter MW, Chellman GJ, Kanapuram S, et al. Investigation of maternal and fetal exposure to an IgG2 monoclonal antibody following biweekly intravaginal administration to cynomolgus monkeys throughout pregnancy. Reprod Toxicol. 2014;48:132-137.

20. Bancroft AJ, Artis D, Donaldson DD, Sypek JP, Grencis RK. Gastrointestinal nematode expulsion in IL-4 knockout mice is IL-13 dependent. Eur J Immunol. 2000;30(7):2083-2091.

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

22. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 2010;8:18.

23. Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113(5):832-836.

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

25. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007; 164(7):1035-1043.

26. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol. 2001;10(1):11-18.

27. Harmonising Outcome Measures for Eczema (HOME). EASI scoring table for aged 8 and over [homepage on the Internet]. Available from: http://www.nottingham.ac.uk/homeforeczema/index.aspx [cited 21-Nov-2016].

28. European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. Consensus report of the European task force on atopic dermatitis. Dermatology. 1993;186(1):23-31.

29. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-216.

30. Greiner W, Weijnen T, Nieuwenhuizen M, Oppe S, Badia X, Busschbach J, et al. A single European currency for EQ-5D health states. Results from a six-country study. Eur J Health Econ. 2003;4(3):222-231.

31. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol. 2004;140(12):1513-1519.

32. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-370.

33. Menactra® Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine [package insert]. Swiftwater, Pennsylvania, US: Sanofi Pasteur, Inc. 2017 [version 0.18 dated 16-Sep-2016; cited 14-Feb-2018]. Available from the US FDA's website.

34. Boostrix® (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed). [package insert]. Research Triangel Park, North Carolina: GlaxoSmithKline [cited 14-Feb-2018]. Available from the US FDA's website.

35. European Parliament and Council of The European Union. Directive 2001/20/EC of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [2001], article 10.

36. Blauvelt A, Simpson E, Wu R, Akinlade B, Graham N, Pirozzi G, et al. The effect of dupilumab on vaccine antibody responses in adults with moderate-to-severe atopic dermatitis; a randomized, double-blind, placebo-controlled trial. Allergy. 2016;71(Suppl.102):95. DOI: 10.1111/all.12971.

37. Chioato A, Noseda E, Stevens M, Gaitatzis N, Kleinschmidt A, Picaud H. Treatment with the interleukin-17A-blocking antibody secukinumab does not interfere with the efficacy of influenza and meningococcal vaccinations in healthy subjects: results of an open-label, parallel-group, randomized single-center study. Clin Vaccine Immunol. 2012;19(10):1597-1602.

38. World Medical Association 2013. Declaration of Helsinki – ethical principles for medical research involving human subjects. 7th (Fortaleza) amendment.

39. International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition. Geneva. Council for International Organizations of Medical Sciences (CIOMS); 2016.

40. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2016. Integrated addendum to ICH E6(R1): Guideline for good clinical practice E6(R2).

41. World Health Organization. WHO model prescribing information: drugs used in skin diseases. Geneva. 1997.

Appendix 1: Definitions of adverse events and serious adverse events

Adverse event definition

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

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavourable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures unless these were planned before the subject consented to trial participation.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 11.4.5).

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 broncospasm, blood dyscrasias and convulsions that do not result in hospitalisation, development of drug dependency or drug abuse.

Adverse events of special interest are described in Section 13.6.1.

Appendix 2: Classification of adverse events

Severity

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

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

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

Causality

The *causal relation* of the AE to the use of the IMP (tralokinumab/placebo) should be described in terms of probable, possible, or not related according to the investigator's clinical judgement. The categories are defined below. Similarly, the causal relationship to each of the vaccines should be evaluated using the categories defined below (that is, probably related, possibly related, or not related).

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

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

Outcome

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

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

Note that as per the above definition, LEO uses “recovered/resolved” only if an event has actually stopped. According to the CDISC definition, the category “recovered/resolved” also includes events which have improved. However, following the LEO definitions above, such an improved event will instead be classified as “not recovered/not resolved” or “recovering/resolving”.

Similarly, it should be noted that as per the above definition, LEO uses “recovered/resolved with sequelae” only if an event has reached a state where the residual symptoms are assumed to persist. According to CDISC, an event is considered “with sequelae”, if it has “retained pathological conditions”. Consequently, it is likely that some of the events classified by LEO with the outcome “recovered/resolved with sequelae” could have been classified with the outcome “recovered/resolved” according to the CDISC definition.

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

Appendix 3: Trial governance considerations

Appendix 3A: Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki (38) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (39).
- Current version of applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines (40).
- EU's General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

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

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

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

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

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

Appendix 3B: Informed consent process

Subjects will receive written and verbal information concerning the clinical trial. This information will emphasise that participation in the clinical trial is voluntary and that the subject may withdraw from the clinical trial at any time and for any reason. All subjects will be given an opportunity to ask questions and will be given sufficient time to consider before consenting.

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

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

A copy of the ICF(s) must be provided to the subject.

Subject card

At screening, subjects will be provided with a card stating that they are participating in a clinical trial and which contains contact address(es) and telephone number(s) of relevant trial site staff, including the number for the investigator in case of emergency situations. The subject card also includes a local telephone number for the emergency unblinding CRO to be used if the investigator or delegated site staff cannot be reached or if unblinding in the IRT cannot be performed.

Appendix 3C: Subject and data confidentiality

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

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

Trial subjects will be assigned a unique identifier (subject ID) by LEO. Any subject's records or datasets that are transferred to LEO will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

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

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

Processing of personal data
This protocol specifies the personal data on trial subjects (for example race, ethnicity, age, gender, health condition, medical history, test results, 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, including but not limited to the EU General Data Privacy Regulation.

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

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

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

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

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

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

- Date(s) of conducting the informed consent process, including date of provision of subject information.
- A statement from the investigator to verify that each of the eligibility criteria are met and documented.
- Subject ID.
- The fact that the subject is participating in a clinical trial in AD including treatment with tralokinumab or placebo for 30 weeks.
- Other relevant medical information.

Trial monitoring

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

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

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

Protocol compliance
Protocol deviations will be documented and notified to the investigator. 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 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. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as LEO staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, verify and reproduce any records and reports that are important to the evaluation of the trial. If the trial site is contacted for an inspection by competent authorities, LEO must be notified immediately.

Risk assessment
In this trial, overall risks have been assessed to ensure subject safety.

Risk reduction activities for the primary endpoints include:

- Sourcing the vaccines to all participating trial sites.
- Monitoring vaccine storage during the trial.
- Ensuring accountability for each vaccine given to subjects.
- Providing trial sites with a laboratory manual which explains how to collect and process blood samples.
- Using validated methods and a central laboratory to assess vaccine responses.

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

Throughout the trial, data quality review meetings will be held to ensure that data collection can be improved and mistakes prevented. During monitoring visits to the trial sites, CRAs will verify that investigators work according to the protocol.

Data handling
Data will be collected by means of electronic data capture unless transmitted electronically to LEO or designee (e.g., laboratory data). The investigator or staff authorised by the

investigator will enter subject data into an eCRF. Data recorded in the eCRFs will be accessible to the trial site and LEO personnel immediately after entry. The eCRFs must be maintained in an up-to-date state by the trial site at all times.

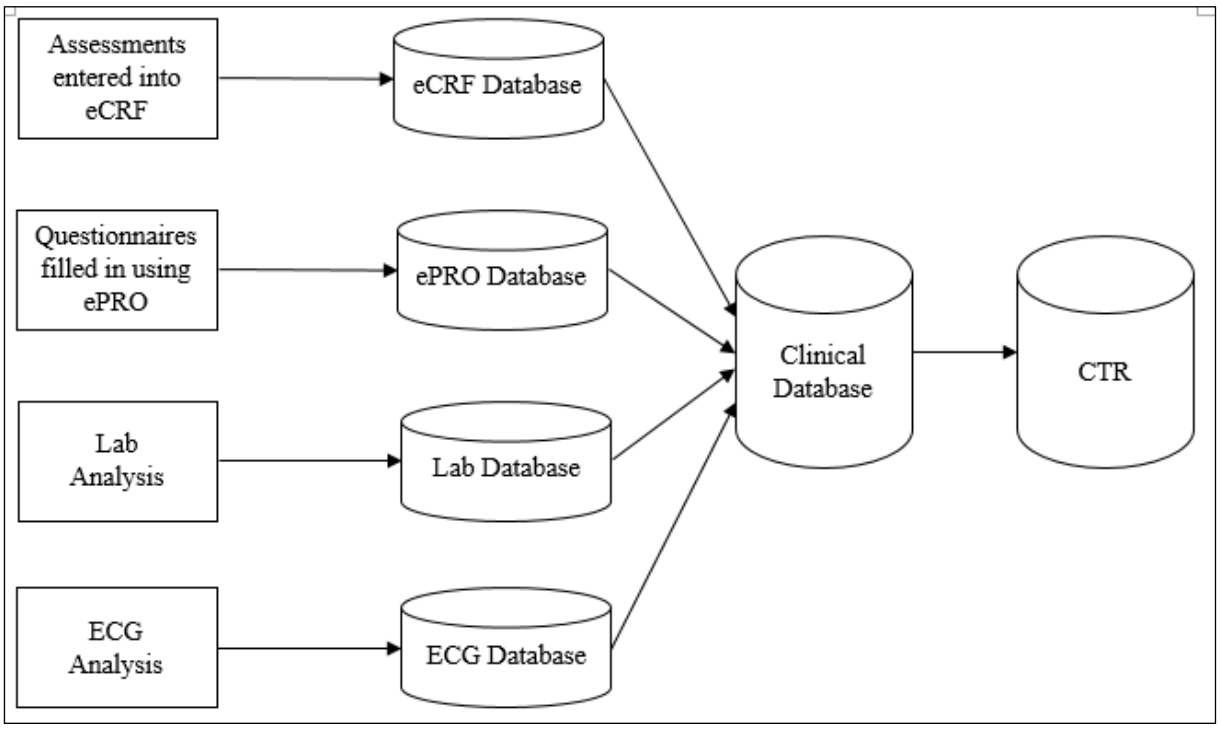
The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRFs used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original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

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

An ePRO solution will be used to capture patient-reported data (data from questionnaires completed at the trial site). By the use of an ePRO, data will be available immediately after data entry and available for monitors and site personnel, including the investigator, with read access only. The ePRO system is a separate application from the eCRF and data captured from the eCRF and the ePRO will be stored on different servers during data capture. Data from both systems will be included in the final trial database.

External data transfers from vendors to LEO will be transmitted and handled via a secure file transfer protocol site. Transmissions of electronic data from external data providers and of ePRO data to the clinical database are illustrated in Panel 14.

Panel 14: Transmission of electronic data



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

Archiving of trial documentation

The investigator at each trial site must make arrangements to store the essential trial documents, including the investigator trial file (40). Essential trial documents must be stored until LEO informs the investigator that the documents are no longer to be retained, or longer if required by local regulations.

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

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

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

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

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

Appendix 3E: Registration, reporting and publication policy

Trial disclosure

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

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

Results of this clinical trial will be posted on the corporate website of LEO in accordance with LEO's Position on Public Access to Clinical Trial Information no later than 12 months after trial completion. Trial results may also become reported in www.ClinicalTrials.gov, www.clinicaltrialsregister.eu and national data registries in accordance with applicable law and regulations after clinical trial completion or premature termination.

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

Publications

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

A multi-centre publication will be submitted for publication within 18 months after the clinical trial has been completed or terminated at all trial sites and all data have been received, defined as database lock of the clinical trial. After such multi-centre publication is made public, or if no multi-centre publication has been submitted with the above-described deadline, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements:

Prior to submission for publication or presenting a manuscript relating to the clinical trial, the investigator shall provide to LEO a copy of all such manuscripts and/or presentations. LEO shall have rights to review and comment. The investigator shall consider LEO's comments but is not required to modify the manuscript and/or presentation based on such comments,

provided, however, that the investigator upon the request of LEO remove any confidential information (other than results generated by the investigator) prior to submitting or presenting the manuscripts. The investigator shall, upon the request of LEO withhold the publication or presentation to allow LEO to protect its inventions and other intellectual property rights described in any such manuscripts.

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

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

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

LEO complies with GPP3 standards and the recommendations from the International Committee of Medical Journal Editors. LEO complies with the positions of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), and the joint position statement by the American Medical Writers Association (AMWA), the European Medical Writers Association (EMWA), and the International Society for Medical Publication Professionals (ISMPP) on disclosure of information about clinical trials, trial results and authorship. LEO also follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines (22).

Appendix 3F: Insurance

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

Appendix 3G: Financial disclosure

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

Appendix 3H: Trial and site closure

Premature termination of trial or trial site

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

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

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

Reasons for the 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 or local health authorities, LEO's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.

Completion of trial

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

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

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

Appendix 3I: Responsibilities

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

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

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

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

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

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

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

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

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

Appendix 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 recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to >95% of all cases of anaphylaxis (for all 3 categories).

Clinical criteria for diagnosing anaphylaxis

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

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

AND AT LEAST ONE OF THE FOLLOWING:

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

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   - Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   - Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Appendix 6: Short version of eligibility criteria

This appendix provides a short form (maximum 200 characters) of each of the eligibility criteria to be used when data are submitted to the FDA.

No.	Inclusion criteria
1	Written informed consent has been obtained prior to any protocol-related procedures
2	Age 18 to 54 years, both included, at screening
3	Diagnosis of AD (as defined by Hanifin and Rajka (1980) criteria for AD)
4	History of AD for 1 year or more
5	Subjects with inadequate response to treatment with topical medications within 1 year before the screening visit or for whom topical treatments are otherwise medically inadvisable
6	AD involvement of 10% (or more) body surface area at screening and baseline (visit 3) according to component A of SCORAD
7	An EASI score of 12 (or more) at screening and 16 (or more) at baseline
8	An IGA score of 3 or more at screening and at baseline
9	Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation
10	Women of childbearing potential must use a highly effective form of birth control, confirmed by the investigator, throughout the trial and at least for 16 weeks after last administration of IMP

No.	Exclusion criteria
1	Concurrent enrolment in another clinical trial where the subject is receiving an IMP
2	Previous randomisation in tralokinumab trials
3	Subjects for whom administration of the meningococcal vaccine provided in this trial is contraindicated or medically inadvisable, according to local label of the vaccine
4	Subjects for whom administration of the tetanus, diphtheria, and pertussis vaccine provided in this trial is contraindicated or medically inadvisable, according to local label of the vaccine
5	Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis
6	Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD

No.	Exclusion criteria
7	Use of tanning beds or phototherapy (NBUVB, UVB, UVA1, PUVA), within 6 weeks prior to randomisation
8	Treatment with immunomodulating medications, systemic corticosteroids, or 3 or more bleach baths during any week within 4 weeks prior to randomisation
9	Treatment with the topical medications TCS, TCI or PDE-4 inhibitor within 2 weeks prior to randomisation
10	Receipt of any vaccine within 3 months prior to screening, any meningococcal vaccine within 1 year prior to screening, or any tetanus-containing vaccine within 5 years prior to screening
11	Receipt of any marketed or investigational biologic agents (e.g., cell-depleting agents or dupilumab) within 6 months prior to randomisation or until cell counts return to normal, whichever is longer
12	Receipt of any investigational non-biologic agent within 5 half-lives prior to randomisation
13	Receipt of blood products within 4 weeks prior to screening
14	Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period
15	Known or suspected allergy or reaction to any component of the IMP formulation
16	History of any active skin infection within 1 week prior to randomisation
17	History of a clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to randomisation
18	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
19	History of anaphylaxis following any biological therapy
20	History of immune complex disease
21	History of cancer
22	Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care
23	History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications
24	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
25	History of attempted suicide or at significant risk of suicide (either in the opinion of the investigator or on the C-SSRS)

No.	Exclusion criteria
26	Any disorder which is not stable and in the investigator's opinion could affect the safety of the subject, influence the findings of the trial, or impede the subject's ability to complete the trial
27	Any abnormal finding which in the investigator's opinion may put the subject at risk, influence the results of the trial, or influence the subject's ability to complete the trial
28	Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level 2.0 times the ULN (upper limit of normal) or more at screening
29	Positive HBsAg, HBsAb, HBcAb or anti-HCV serology at screening. Subjects with positive HBsAb may be randomised provided they are hepatitis B vaccinated and have negative HBsAg and HBcAb
30	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
31	Subjects who are legally institutionalised
32	Pregnant, breastfeeding, or lactating women
33	Employees of the trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals

Appendix 7: Contact list

Contact details for the clinical project manager, appointed CRA, sponsor's medical expert, vendors used in the trial, and national coordinating investigators 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

Appendix 8: WHO model prescribing information for classification of topical corticosteroids

Hydrocortisone and betamethasone are examples of low- and high-potency TCS. TCS have been ranked in terms of potency into 4 groups consisting of 7 classes. Class I TCS are the most potent and Class VII TCS are the least potent (Panel 15). Efficacy and side-effects are greatest with the Class I ultra-high-potency preparations which should only be used for limited time periods (2-3 weeks).

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

Panel 15: Classification of topical corticosteroids

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

Panel 15: Classification of topical corticosteroids (continued)

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

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

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