Cover Page

Study title: Long-term Extension Trial in Subjects With Atopic Dermatitis Who Participated in Previous Tralokinumab Trials - ECZTEND
LEO Pharma number: LP0162-1337
NCT number: NCT03587805
Date: 21-Feb-2022

Updated Clinical Trial Protocol

LP0162-1337

Long-term extension trial in subjects with atopic dermatitis who participated in previous tralokinumab trials – ECZTEND

Phase 3 – long-term extension trial

An open-label, single-arm, multi-centre, long-term extension trial to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials

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

LEO Pharma A/S	**Trial ID:**	**LP0162-1337**
	Date:	**21-Feb-2022**
	EudraCT no:	**2018-000746-19**
	Version:	**14.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

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

PPD MSc Stat
PPD Medical Sciences

PPD MD
PPD Medical Sciences

PPD MD, PhD
PPD Medical Sciences

PPD MSc Pharm
PPD Global Clinical Operations

PPD , BN, RN, MIND
PPD Qualified Person for Pharmacovigilance

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:

PPD MD, MBA
Signatory investigator

Acknowledgement statement investigator(s)

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

Protocol amendment summary of changes table

Document history:

Document	Date	Type of protocol amendment
Amendment 10 (non-substantial) (protocol version 14.0)	21-Feb-2022	Global
Amendment 9 (substantial) (protocol version 13.0)	08-Feb-2022	Global
Amendment 2 DE (substantial) (protocol version 12.0 DE)	22-Mar-2021	Local (DE, applicable for subjects from the 1 site of the parent trial TRA-WEI-0015-I)
Amendment 2 JP (substantial) (protocol version 12.0 JP)	22-Mar-2021	Local (JP)
Amendment 8 (non-substantial) (protocol version 11.0)	12-Feb-2021	Global
Amendment 7 (substantial) (protocol version 10.0)	25-Nov-2020	Global
Amendment 1 DE (substantial) (protocol version 9.0 DE)	03-Nov-2020	Local (DE, to add parent trial TRA-WEI-0015-I)
Amendment 1 JP (substantial) (protocol version 9.0 JP)	22-Oct-2020	Local (JP, to add parent trial LP0162-1343)
Amendment 6 (substantial) (protocol version 8) (protocol version 7.0 was made obsolete)	17-Feb-2020	Global
Amendment 5 (non-substantial) (protocol version 6.0)	24-Jun-2019	Global
Amendment 4 (substantial) (protocol version 5.0)	28-May-2019	Global
Amendment 3 (substantial) (protocol version 4.0)	13-Dec-2018	Global

Amendment 2 (substantial) (protocol version 3.0)	31-Aug-2018	Global
Amendment 1 (substantial) (protocol version 2.0)	27-Jun-2018	Global
Original protocol (protocol version 1.0)	01-Jun-2018	NA

Amendment 10 (21-Feb-2022)

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

Overall rationale for amendment 10:

The main reason for amendment 10 is to correct the visit window back to ±3 days in Panel 5. This was by mistake changed to ±7 days in amendment 9. Changes introduced with amendment 9 are presented below.

Amendment 9 (08-Feb-2022)

Amendment 9 is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union or subsequent regulation.

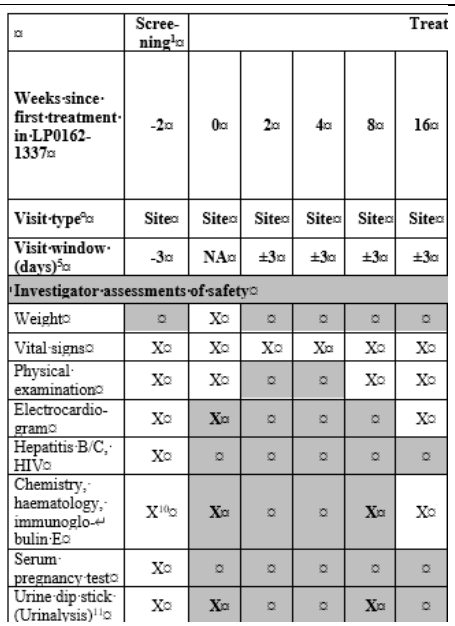
Overall rationale for amendment 9:

The main reason for amendment 9 is to shorten the safety follow-up period from 16 weeks to 4 weeks for subjects transferred from the adolescent parent trial LP0162-1334. Furthermore, changes that were made for the local protocol versions for Japan and Germany have been implemented in the protocol, and the definition of treatment completers has been updated.

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

The table below describes the changes in each section, summarised as plain text, and/or as tracked changes (text added to the protocol is written in **bold** and deleted text ~~has a line through it~~).

Section no. and name	Description of change	Brief rationale
Whole document	Protocol versions in-text have either been deleted or reworded to avoid stating the protocol version, or updated to e.g. 'prior to protocol version 10' or 'protocol versions 10 to 13'.	Update to correspond to the applicable versions of the protocol.
1 Protocol synopsis 3 Schedule of trial design 4 Schedule of trial procedures 7.1 Overall trial design	For subjects transferred from the adolescent parent trial LP0162-1334, the safety follow-up period has been shortened from 16 weeks to 4 weeks.	To offer a shorter safety follow-up period for the adolescent subjects to allow subjects the possibility of treatment prior to complete wash-out of tralokinumab. This is possible as no safety concerns were identified in the parent trial.
4.2 ECZTEND - schedule of trial procedures after May 2021 Panel 5 ECZTEND -schedule of trial procedures for subjects who re-consent/consent to participate in the trial after May 2021	In alignment with the schedule of trial procedures until end of May 2021, the timings of the electrocardiogram, chemistry, haematology, immunoglobulin E, and urine dipstick assessments during the first 8 weeks in the schedule of trial procedures after May 2021 have been corrected as follows: • Electrocardiogram: addition of assessments at Week 0. • Chemistry, haematology, immunoglobulin E: addition of assessments at Weeks 0 and 8. • Urine dipstick: addition of assessments at Weeks 0 and 8.	The electrocardiogram, chemistry, haematology, immunoglobulin E, and urine dipstick assessments during the first 8 weeks in the trial must be the same for all included subjects to be able to sufficiently monitor the safety of subjects.

Section no. and name	Description of change	Brief rationale
		
5.2 Experience with investigational medicinal product	The AD development programme investigates tralokinumab in subjects with moderate-to-severe AD. To date, **9** clinical trials have been completed: a phase 2b dose-finding trial (trial D2213C00001), 2 phase 3 trials with tralokinumab as monotherapy (LP0162-1325 and LP0162-1326), a phase 3 trial with tralokinumab in combination with TCS (LP0162-1339), a phase 2 vaccine response trial (LP0162-1341), **a phase 3 trial in adolescent subjects (LP0162-1334), a phase 1 drug-drug interaction trial (LP0162-1342), a phase 3 trial in adult subjects with severe AD ineligible to treatment with cyclosporin A (LP0162-1346), and a phase 3 trial with tralokinumab in combination with TCS (LP062-1343) in Japanese subjects with moderate-to-severe AD who are candidates for systemic therapy.**	To provide information on the current status of the AD development programme for tralokinumab.
7.3 End of trial definition	**The duration of the treatment period for each subject will depend on when the**	To update the definition of

Section no. and name	Description of change	Brief rationale
	subject enters the trial after completing the parent trial, and by which treatment stop date they have consented to (end of May 2021, end of May 2022, or a country-specific end of treatment day according to Appendix 3J). Hence, a subject is considered to have completed the treatment period **for either of the following scenarios**: ~~if the subject has completed the EOT visit with no 'primary reason for withdrawal from trial'. This will be:~~ • Approximately end of May 2021 for subjects completing according to **earlier versions than** protocol version **10** ~~or earlier versions~~. • Approximately end of May 2022 for subjects from the parent trial LP0162-1334 **who consented to continue in the trial after May 2021** ~~completing according to protocol version 11~~. • At a country-specific end of treatment date (Appendix 3J) for subjects from the parent trials LP0162-1325, -1326, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I **who consented to continue in the trial after May 2021** ~~completing according to protocol version 11~~.	treatment completers.
8.3 Exclusion criteria	Receipt of inactive/killed vaccines (for example, inactive influenza and **inactive COVID-19** vaccines) is allowed, provided they are not administered within 5 days before/after any IMP injection.	To specify that for COVID-19 vaccines, only inactive vaccines are allowed.
9.10 Reporting product complaints	The fax number for Global Safety, LEO Pharma has been changed:	To provide information on

Section no. and name	Description of change	Brief rationale
13.4.1 Investigator reporting responsibilities	**Fax number: +45 6910 2468**	updated contact information for Global Safety, LEO Pharma
11.4.5.3 Investigator evaluation of laboratory samples	Urine samples will be tested at the trial site with a dipstick. ~~If the dipstick shows any~~ **Until end of May 2021, in case of** abnormal **dipstick results** ~~reading~~**, a urine sample was** ~~must always be collected and~~ sent to the central laboratory **for microscopic examination (leucocytes, erythrocytes, and casts).** ~~further analysis, regardless of causality or local assessment of significance~~ **After May 2021, a urine sample will only be sent to the central laboratory to perform urinalysis if considered required by the investigator based on the urine dipstick results.**	To correct the discrepancy between Section 4.2 footnote no. 11 and text in Section 11.4.5.3 regarding testing of urine samples.
11.8 End of trial	An end of treatment form must be completed in the eCRF for all subjects ~~assigned to~~ **completing** treatment. The following data will be collected: • Date of last administration of IMP.	To correct error.
13.6.6 Aggravation of condition	~~Any clinically significant aggravation/exacerbation/worsening of any medical condition (including the trial disease), compared with baseline, must be reported as an AE. If the AE qualifies as an SAE, expedited reporting is required (Section 13.4).~~ **Any clinically significant aggravation/exacerbation/worsening of any medical condition(s) (including the trial disease), compared with baseline, must be reported as an (S)AE in accordance with Sections 13.3 and 13.4.**	To correctly specify the reporting of aggravation of condition.

<table>
<tr><th>Section no. and name</th><th>Description of change</th><th>Brief rationale</th></tr>
<tr><td></td><td>AD is a fluctuating disease with possible periods of remission. In case of relapses/recurrences, only aggravations/exacerbations exceeding normal disease fluctuation or lesions appearing in a body area normally not affected by AD should be reported as an AE.</td><td></td></tr>
<tr><td>Appendix 3J

Panel 17</td><td>Subjects from the parent trial LP0162-1334, who consented to participate in the trial ~~based on protocol version 11~~ after May 2021, will end treatment by end of May 2022 in all countries.

Subjects from the parent trials LP0162-1325, -1326, -1339, -1341, -1342,-1343, -1346, and TRA-WEI-0015-I, who consented to participate in the trial after May 2021 ~~based on protocol version 11~~, will have a country-specific end of treatment date (Panel 17).

Panel 17: Country-specific last subject last treatment for parent trials LP0162-1325, -1326, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I
<table>
<tr><td>Country</td><td>Approximate last treatment date in the trial*</td></tr>
<tr><td>US</td><td>May 2022</td></tr>
<tr><td>Germany</td><td>Aug 2021</td></tr>
<tr><td>UK</td><td>Sep 2022</td></tr>
<tr><td>France</td><td>Aug 2022</td></tr>
<tr><td>Italy</td><td>Jan 2023</td></tr>
<tr><td>Belgium</td><td>Nov 2022</td></tr>
<tr><td>Canada</td><td>May 2023</td></tr>
<tr><td>Spain</td><td>Jan 2023</td></tr>
<tr><td>Poland</td><td>May 2024</td></tr>
<tr><td>Czech Republic</td><td>Oct 2022</td></tr>
<tr><td>Japan</td><td>May 2023</td></tr>
</table>
*These dates are estimates of availability of tralokinumab in the countries and could change.</td><td>To update the country-specific end dates according to expected availability of tralokinumab in the countries.</td></tr>
<tr><td>Throughout</td><td>Minor editorial revisions.</td><td>Minor, have therefore not been summarised.</td></tr>
</table>

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List of panels

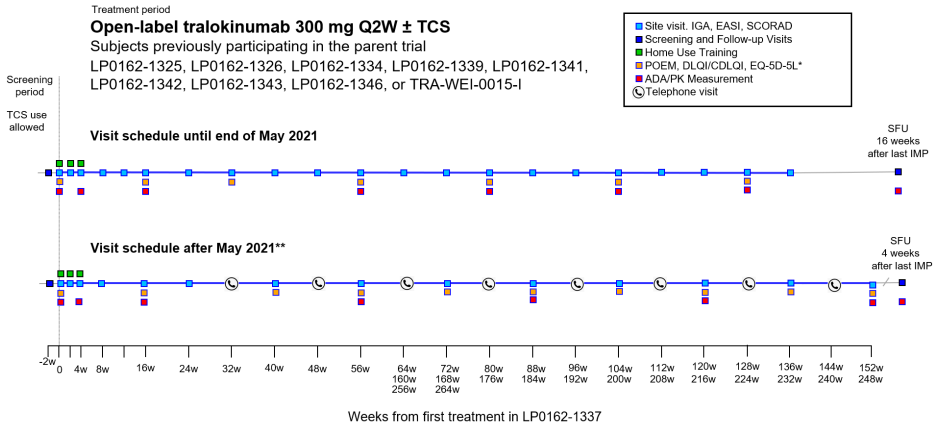
List of abbreviations

AD	atopic dermatitis
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
CCL	C-C motif chemokine
CCL17	C-C motif chemokine 17 (also known as TARC)
CDER	United States Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDLQI	Children's Dermatology Life Quality Index
CMO	contract manufacturing organisation
COVID-19	Coronavirus Disease 2019
CRA	clinical research associate
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	clinical trial report
CXCL 10	C-X-C motif chemokine ligand 10
CYP	cytochrome P450
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI75/50	at least 75% / 50% reduction in EASI score
ECG	Electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
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
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IEC	independent ethics committee

IFNG	interferon gamma
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IL	Interleukin
IMP	investigational medicinal product
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
nAB	neutralising antibodies
NIMP	non-investigational medicinal product
NRS	numeric rating scale
PK	pharmacokinetics
POEM	Patient Oriented Eczema Measure
PDE-4	phosphodiesterase 4
PRO	patient-reported outcome
Q2W	every second week
qPCR	quantitative real time polymerase chain reaction
S100A9	S100 calcium-binding protein A9
S100A12	S100 calcium-binding protein A12
SAE	serious adverse event
SC	subcutaneous(ly)
SCORAD	Scoring Atopic Dermatitis
SD	standard deviation
SFU	safety follow-up
SOC	system organ class
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
UC	ulcerative colitis
UK	United Kingdom
US	United States

1 Protocol synopsis

<table>
<tr><td>Trial ID
EudraCT no.
IND no.
FDA center</td><td colspan="2">LP0162-1337
2018-000746-19
123797
CDER</td></tr>
<tr><td>Title of trial</td><td colspan="2">An open-label, single-arm, multi-centre, long-term extension trial to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials – ECZTEND</td></tr>
<tr><td>Short title of trial</td><td colspan="2">Long-term extension trial in subjects with atopic dermatitis who participated in previous tralokinumab trials – ECZTEND</td></tr>
<tr><td rowspan="4">Main objectives and endpoints</td><td>Primary objective</td><td>Primary endpoint</td></tr>
<tr><td>To evaluate the long-term safety of tralokinumab</td><td>• Number of adverse events during the treatment period from baseline up to Week 268</td></tr>
<tr><td>Secondary objective</td><td>Secondary endpoint</td></tr>
<tr><td>To evaluate the efficacy of tralokinumab given as continuous treatment, re-treatment, or introduced for the first time in tralokinumab-naïve subjects</td><td>• Investigator’s Global Assessment (IGA)[1] score of 0 (clear) or 1 (almost clear) at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248
• At least 75% reduction in Eczema Area and Severity Index (EASI75)[2] relative to baseline in parent trial, at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248</td></tr>
<tr><td colspan="2">[1] The IGA is an instrument used in clinical trials to rate the severity of the subject's global atopic dermatitis (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 or more extensive condition.</td></tr>
<tr><td>Final collection of data for the primary endpoint</td><td colspan="2">The final collection of data for the primary endpoint will occur by Q2 2024.
• For subjects who did NOT re-consent to participate in the trial after May 2021, the final collection of data for the primary endpoint occurred at Week 140 or earlier, dependent on when they were included in the trial.
• For subjects from the adolescent parent trial LP0162-1334 who consented to participate in the trial after May 2021, treatment was extended by 1 year until end of May 2022. For these subjects, the final collection of data for the primary endpoint will occur at Week 114 or earlier.
• For subjects from the parent trials LP0162-1325, -1326, -1339, -1341,-1342, -1343, -1346, and TRA-WEI-0015-I (investigator-initiated trial) who consented to participate in the trial after May 2021, trial treatment will be stopped at a country-specific treatment</td></tr>
</table>

	completion date. For these subjects, the final collection of data for the primary endpoint will occur at Week 268 or earlier.
Trial design	The trial will include a screening period of 2 weeks (Week -2 to Week 0), and a long-term treatment period of approximately 0.5 to 5.0 years. The duration of the treatment period for each subject will depend on when the subject enters the trial after completing the parent trial, and by which treatment stop date they have consented to (end of May 2021, end of May 2022, or a country-specific end of treatment day).  **Notes:** * Subjects from the parent trial LP0162-1334 will not perform the EQ-5D-5L. ** Visit schedule after May 2021 applies to subjects who consented to continue in the trial after May 2021, or who are included in the trial after May 2021. Treatment will be ended at a country-specific treatment end date (see Appendix 3J), or by end of May 2022 (subjects from the parent trial LP0162-1334). **Abbreviations:** ADA = anti-drug antibodies; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5D-5L = EuroQoL 5 Dimension Health Questionnaire 5-Level; IGA = Investigator's Global Assessment; IMP = investigational medicinal product; PK = pharmacokinetics; POEM = Patient Oriented Eczema Measure; Q2W = every second week; SCORAD = Scoring Atopic Dermatitis; SFU = safety follow-up; TCS = topical corticosteroids; w = weeks. Subjects included in the trial prior to protocol version 10 attended site visits every 8 weeks until end of May 2021. For subjects who did NOT re-consent to continue in the trial after May 2021, trial treatment was ended end of May 2021. Subjects who re-consented to continue in the trial after May 2021 and subjects who consent to be included in the trial based on protocol versions 10 to 13 will follow a modified trial visit schedule more similar to standard practice for home use. The modified trial schedule consists of 2 types of site visits (standard site visits and short site visits), interchanging with a mandatory telephone visit between the site visits. Dependent on the subject's consent, subjects included or who continued after May 2021 complete treatment by end of May 2022 (subjects from LP0162-1334) or at a country-specific treatment end date between August 2021 and May 2024, to ensure continued treatment of subjects until treatment with tralokinumab is also available to patients outside the clinical trial setting. After adequate training by site staff at the first 3 visits, subjects will inject tralokinumab 300 mg every 2 weeks at home (or have tralokinumab injected by a caregiver) during the treatment period. All subjects will use an emollient twice daily (or more, as needed) for at least 14 days before baseline and will continue this treatment throughout the trial,

	including the safety follow-up period. Subjects can use TCS (US class ≥4 or Europe class ≤3) or TCI at the investigator's discretion.
Main assessments	Safety assessments Adverse event reporting, anti-drug antibodies, vital signs, physical examination, electrocardiograms, and laboratory tests. Efficacy assessments IGA and EASI.
Main criteria for inclusion	• Completed the treatment period(s) of one of the parent trials: LP0162-1325, -1326, -1334, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I. • Complied with the clinical trial protocol in the parent trial to the satisfaction of the investigator. • Able and willing to self-administer tralokinumab treatment (or have it administered by a caregiver) at home after the initial 3 injection visits at the trial site (in this trial). • Stable dose of emollient twice daily (or more, as needed) for at least 14 days before baseline.
Main criteria for exclusion	• Any condition that required permanent discontinuation of trial treatment in the parent trial. • More than 26 weeks have elapsed since the subject received the last injection of investigational medicinal product (IMP) in the parent trial (to be assessed at baseline). • Subjects who, during their participation in the parent trial, developed a serious adverse event (SAE) deemed related to tralokinumab by the investigator, which in the opinion of the investigator could indicate that continued treatment with tralokinumab may present an unreasonable safety risk for the subject. • Subjects who, during their participation in the parent trial, developed an AE that was deemed related to tralokinumab by the investigator and led to temporary discontinuation of trial treatment, which in the opinion of the investigator could indicate that continued treatment with tralokinumab may present an unreasonable safety risk for the subject. • Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroids within 5 half-lives prior to baseline. • Treatment with topical phosphodiesterase 4 inhibitors or topical JAK inhibitors within 2 weeks prior to baseline. • Receipt of any marketed biological therapy (that is, immunoglobulin or anti-immunoglobulin E) including dupilumab or investigational biologic agents: o Any cell-depleting agents, including but not limited to rituximab: within 6 months prior to baseline, or until lymphocyte count returns to normal, whichever is longer. o Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline. • Clinically significant infection within 4 weeks prior to baseline.

	• A helminth parasitic infection within 6 months prior to the date when informed consent is obtained. • Tuberculosis requiring treatment within 12 months prior to screening. • Known primary immunodeficiency disorder.
Investigational medicinal product	• Name/active substance: tralokinumab (human recombinant IL-13 monoclonal antibody of the immunoglobulin G4 subclass that specifically binds to human IL-13 and blocks interaction with the IL-13 receptors). • Dosage form: solution (in accessorised pre-filled syringe, 1.0 mL fill volume). • Concentration: 150 mg/mL. • Dose for adult subjects from all parent trials, except the parent trial LP0162-1334: 600 mg initial loading dose, then 300 mg every second week. • Dose for subjects from the parent trial LP0162-1334*: 300 mg every second week. *All subjects from the parent trial LP0162-1334, independent of the subject's age when included in ECZTEND. • Method of administration: subcutaneous injection.
Duration of treatment	The duration of the treatment period for each subject will depend on when the subject enters the trial after completing the parent trial, and by which treatment stop date they have consented to (end of May 2021, end of May 2022, or a country-specific end of treatment day): • For subjects who did NOT re-consent to participate in the trial after May 2021, trial treatment was stopped by end of May 2021. Treatment duration was maximum 140 weeks. • For subjects from the parent trial LP0162-1334 who consented to participate in the trial after May 2021, trial treatment will be stopped by end of May 2022. Treatment duration will be maximum 114 weeks. • For subjects from the parent trials LP0162-1325, -1326, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I who consent to participate in the trial after May 2021, trial treatment will be stopped at a country-specific treatment completion date. Treatment duration will be maximum 268 weeks.
Number of subjects	It is assumed that approximately 1,600 subjects will be assigned to treatment.
Number and distribution of trial sites	Approximately 330 sites in Canada, Europe, Japan, and the US.
Statistical methods	<u>Primary endpoint</u> AEs will be summarised for all treated subjects (full analysis set) and will be presented by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and primary system organ class (SOC) as percentage of subjects with AEs, number of AEs, and rate of AEs (number of AEs per 100 patient-years of exposure).

	Secondary endpoints The analyses of the secondary endpoints will be made for the full analysis set as well as for the observed cases. IGA and EASI75 will be presented as response rates with 95% confidence intervals at each assessment visit. The results will be presented for the total cohort of subjects and by tralokinumab-naïve/re-treated/continuously treated subjects. For the re-treated and continuously treated subjects, the results will further be divided by responders/non-responders; clinical response is defined as achievement of IGA 0/1 or EASI75 at the last assessment in the parent trial.
Signatory investigator	PPD
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

2 Trial identification

EudraCT number: 2018-000746-19

IND number: 123797

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

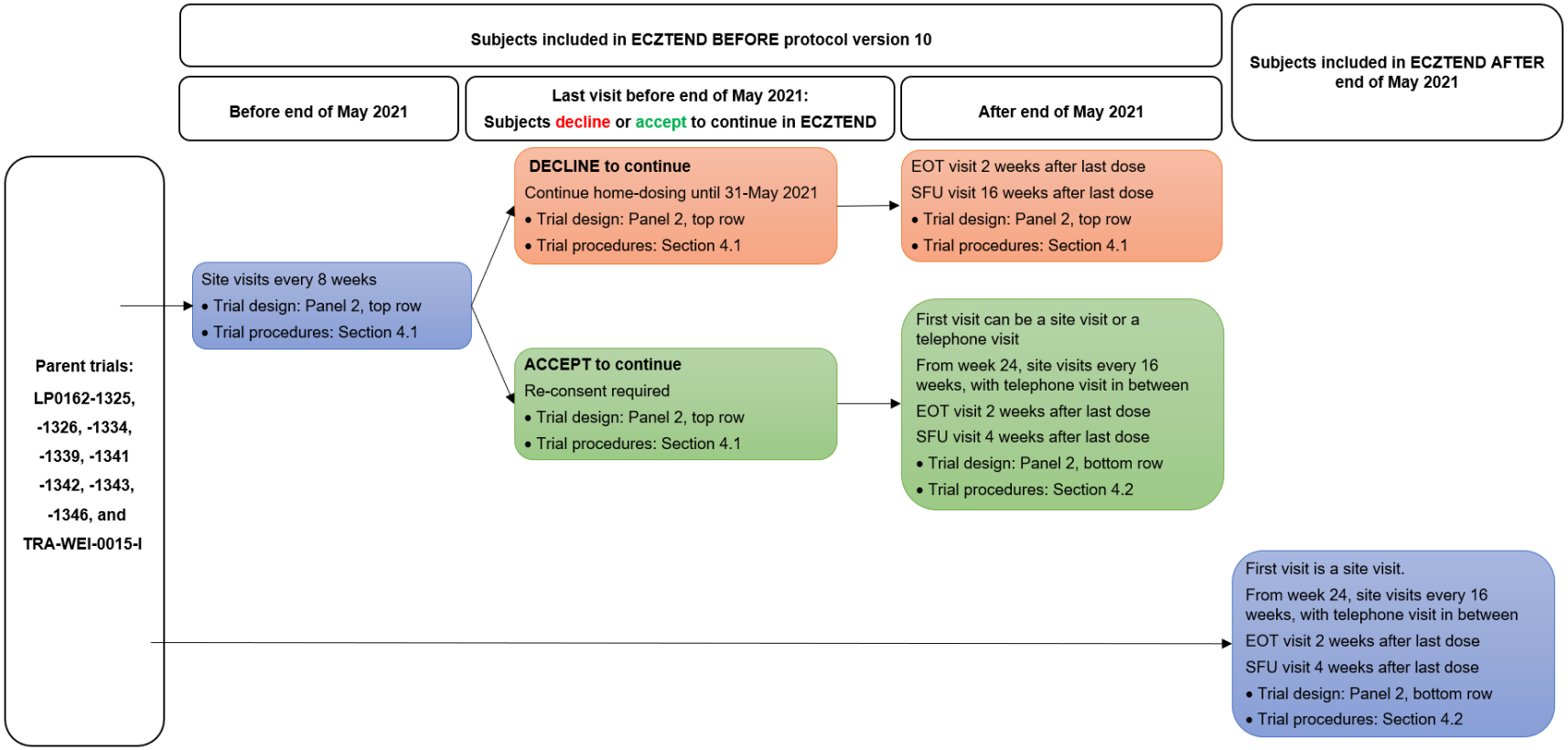
3 Schematic of trial design

An overview illustrating the different scenarios for trial participation (subject did NOT re-consent to continue in the trial after May 2021, subject DID re-consent to continue in the trial after May 2021, or subject was included in the trial after May 2021) is presented in Panel 1.

Panel 2 illustrates the trial design applicable until May 2021 (top row) and after May 2021 (bottom row), where a number of site visits were replaced by mandatory telephone visits for subjects participating in the trial after May 2021 to reduce the burden of frequent site visits. It required a re-consent or consent to participate in the trial after May 2021 (all trials).

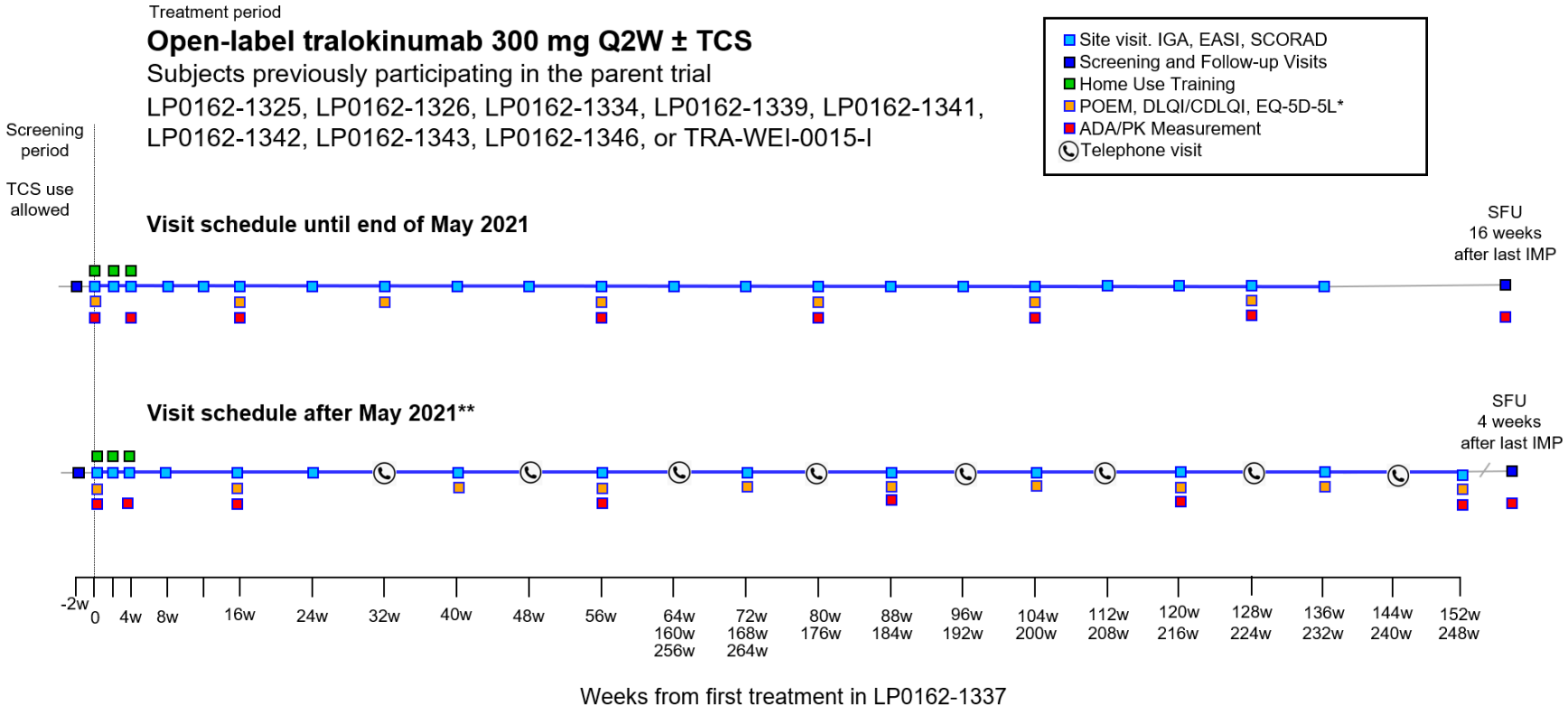
In the case where a subject is unable to attend site visits due to the COVID-19 pandemic, please refer to Appendix 3K for guidance.

Panel 1: Overview of scenarios for trial participation



Abbreviations: EOT = end of treatment; SFU = safety follow-up

Panel 2: Trial design



Notes: Subjects can be included in ECZTEND after completion of the treatment period in the parent trial, and continue with a long-term treatment period of approximately 0.5 to 5 years in ECZTEND. Subjects who did NOT re-consent to participation in the trial after May 2021 stopped IMP treatment by end of May 2021 followed by 16 weeks of SFU (top row visit schedule). * Subjects from the parent trial LP0162-1334 will not perform the EQ-5D-5L. ** Visit schedule after May 2021 applies to subjects who consented to continue in the trial after May 2021, or who are included in the trial after May 2021. Treatment will be ended at a country-specific treatment end date (see Appendix 3J), or by end of May 2022 (subjects from the parent trial LP0162-1334).

Abbreviations: ADA = anti-drug antibodies; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5D-5L = EuroQoL 5 Dimension Health Questionnaire 5-Level; IGA = Investigator's Global Assessment; IMP = investigational medicinal product; PK = pharmacokinetics; POEM = Patient Oriented Eczema Measure; Q2W = every second week; SCORAD = Scoring Atopic Dermatitis; SFU = safety follow-up; TCS = topical corticosteroids; w = weeks.

4 Schedule of trial procedures

In the case where a subject is unable to attend site visits due to the COVID-19 pandemic, please refer to Appendix 3K for guidance.

4.1 ECZTEND - schedule of trial procedures until end of May 2021

Panel 3: ECZTEND - schedule of trial procedures (up to Week 56) until end of May 2021

	Screening[1]	Treatment period[2]											References (protocol section)
Visits	**1+2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Weeks	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**56**	
Visit window (days)[3]	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Trial population and eligibility													
Informed consent[4]	X												Appendix 3B
Subject eligibility	X	X											8.1, 8.2, 8.3
Investigator assessments at screening/baseline only													
Demographics	X												11.2.1
Medical history	X	X											11.2.2
Height		X											11.2.3
Columbia-Suicide Severity Rating Scale	X												11.2.4
Treatments													
Concomitant medication and concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	X	9.6
Initiation of emollient[5]	X												9.4
Tralokinumab administration/dispensing[6]		X[7]	X[7]	X[7]	X	X	X	X	X	X	X	X	9.2, 9.8.3
Treatment compliance		X	X	X	X	X	X	X	X	X	X	X	9.8.4

	Screening[1]	Treatment period[2]											References (protocol section)
Visits	**1+2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Weeks	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**56**	
Visit window (days)[3]	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Investigator assessments of efficacy													
Investigator's Global Assessment		X	X	X	X	X	X	X	X	X	X	X	11.3.1.1
Eczema Area and Severity Index		X	X	X	X	X	X	X	X	X	X	X	11.3.1.2
SCORing Atopic Dermatitis		X	X	X	X	X	X	X	X	X	X	X	11.3.1.3
Investigator assessments of safety													
Weight		X										X	11.4.1
Vital signs	X	X[7]	X[7]	X[7]	X	X	X		X			X	11.4.2
Physical examination	X	X			X		X		X			X	11.4.3
Electrocardiogram	X	X					X		X			X	11.4.4
Hepatitis B/C, HIV	X												11.4.5
Chemistry, haematology, immunoglobulin E	X[8]	X			X		X		X			X	11.4.5
Serum pregnancy test	X												11.4.5
Urinalysis[9]	X	X			X		X		X			X	11.4.5
Urine pregnancy test		X		X	X	X	X	X	X	X	X	X	11.4.5
Anti-drug antibodies		X		X			X					X	11.4.6
Pharmacokinetics blood sample		X		X			X					X	11.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	13
Patient-reported outcomes													
Patient Oriented Eczema Measure		X					X		X			X	11.3.2.1
Dermatology Life Quality Index (DLQI)/CDLQI[10]		X					X		X			X	11.3.2.2

	Screening[1]	Treatment period[2]											References (protocol section)
Visits	**1+2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Weeks	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**56**	
Visit window (days)[3]	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Patient-reported outcomes (continued)													
EuroQoL 5-Dimension Health Questionnaire 5-Level[11]		X					X		X			X	11.3.2.3
Worst Weekly Pruritus numeric rating scale[12] Eczema-related Sleep numeric rating scale[12] Patient use of topical treatment[13]	X	X	X	X	X	X	X	X	X	X	X	X	11.3.2.4
Other assessments													
Skin biopsies[14]											X		11.6

1) If screening/baseline visits are performed on the same day as visit(s) in the parent trial, the order of assessments should be adhered to, working in parallel for both protocols. Assessments where data are captured in different vendor systems databases (ECG, ePRO, and laboratory tests) need to be completed twice. In such cases, the parent trial assessment should be performed first, followed by the trial LP0162-1337 assessment.
2) Subjects who withdraw from the trial will be followed up as described in Section 10. All subjects will have a safety follow-up period of 14 weeks, starting 2 weeks after the last dose of tralokinumab (that is, the final safety follow-up visit will be 16 weeks after the last dose).
3) If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to baseline.
4) The informed consent form must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations; for adolescent subjects participating in ECZTEND, legal representative(s) must sign a legal representative informed consent form and the adolescent subject must sign an informed assent form. Adolescent subjects who become adults during participation in ECZTEND must re-consent by signing the informed consent form for adult subjects. Additional informed consent is required for participation in the exploratory part involving skin biopsy (selected trial sites only).
5) All subjects must use an emollient, as background treatment, twice daily (or more, as needed) for at least 14 days before baseline and must continue this treatment throughout the trial (including safety follow-up).
6) At trial visits, tralokinumab will be injected at the trial site, preferably by the subject or their caregiver, alternatively by site staff. At each trial visit from Week 4 onwards, subjects will be provided with tralokinumab to be administered at home until the next trial visit. In case of intercurrent illness that may

compromise the safety of the subject, or fever within 72 hours prior to administration, tralokinumab administration should be rescheduled. If an anaphylactic reaction occurs, blood samples should be drawn for the analysis of serum tryptase (see details in Section 9.2).

7) At the first 3 tralokinumab dosing visits, subjects (or their caregiver) will be trained in how to inject tralokinumab, except for those who have already been trained in home use during the parent trial. In addition, if the subject and/or the caregiver is/are health care professional(s), no training is required, but the subject should be trained in how to handle the IMP according to the IMP handling manual and in the procedures to be followed in the event of an emergency. At the first 3 dosing visits, subjects (except for those who have received open-label tralokinumab treatment in the parent trial) will also be monitored for immediate drug reactions for a minimum of 30 minutes after dosing, with vital signs taken after 30 minutes or until stable, whichever is later.
8) IgE will not be measured at screening.
9) 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 (leucocytes, erythrocytes, and casts) (Section 11.4.5).
10) Adult subjects from all parent trials, except the LP0162-1334 trial, will perform the DLQI. Subjects from the parent trial LP0162-1334 will perform the CDLQI, independent of the age of the subject during participation in ECZTEND.
11) Subjects from the parent trial LP0162-1334 will not perform the EuroQoL 5-Dimension Health Questionnaire 5-Level.
12) Subjects from the parent trial LP0162-1334 will perform an adolescent's pruritis NRS with a recall period of past 7 days, and an eczema-related sleep NRS with a recall period over the past 7 nights, independent of the age of the subject during participation in ECZTEND.
13) Based on subject recall during the last week prior to each site visit (from 6 days prior to each visit and including the day of the visit).
14) Optional at selected sites and only for subjects who had skin biopsies taken in the parent trial LP0162-1325.

Abbreviations: CDLQI = Children's Dermatology Life Quality Index; ECG = electrocardiogram; ePRO = electronic patient-reported outcome; DLQI = Dermatology Life Quality Index; IMP = investigational medicinal product; NA = not applicable; NRS = numeric rating scale.

Panel 4: ECZTEND - schedule of trial procedures (Week 64–EOT) until end of May 2021

	Treatment period[1]							SFU[1]	Unscheduled visit (if applicable)[3]	Early termination (if applicable)[1]	References (protocol section)
Visits	**14 20**	**15 21**	**16 22**	**17 23**	**18**	**19**	**EOT visit**	**SFU visit**			
Weeks	**64 112**	**72 120**	**80 128**	**88 136**	**96**	**104**	**Variable[2] (max 140)**	**Variable[2]**			
Visit window (days)[4]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Treatments											
Concomitant medication and concurrent procedures	X	X	X	X	X	X	X	X	X	X	9.6
Tralokinumab administration/dispensing[5]	X	X	X	X	X	X			X		9.2, 9.8.3
Treatment compliance	X	X	X	X	X	X	X		X	X	9.8.4
Investigator assessments of efficacy											
Investigator's Global Assessment	X	X	X	X	X	X	X		X	X	11.3.1.1
Eczema Area and Severity Index	X	X	X	X	X	X	X		X	X	11.3.1.2
SCORing Atopic Dermatitis	X	X	X	X	X	X	X		X	X	11.3.1.3
Investigator assessments of safety											
Weight						X	X			X	11.4.1
Vital signs	X	X	X	X	X	X	X	X	X	X	11.4.2
Physical examination			X			X	X	X	X	X	11.4.3
Electrocardiogram			X			X	X	X	X	X	11.4.4
Chemistry, haematology, immunoglobulin E			X			X	X	X	X	X	11.4.5
Urinalysis[6]			X			X	X	X	X	X	11.4.5
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	11.4.5

	Treatment period[1]							SFU[1]	Unscheduled visit (if applicable)[3]	Early termination (if applicable)[1]	References (protocol section)
Visits	**14 20**	**15 21**	**16 22**	**17 23**	**18**	**19**	**EOT visit**	**SFU visit**			
Weeks	**64 112**	**72 120**	**80 128**	**88 136**	**96**	**104**	**Variable[2] (max 140)**	**Variable[2]**			
Visit window (days)[4]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Investigator assessments of safety (continued)											
Anti-drug antibodies			X			X	X	X	X	X	11.4.6
Pharmacokinetics blood sample			X			X	X	X	X	X	11.5
Adverse events	X	X	X	X	X	X	X	X	X	X	13
Patient-reported outcomes											
Patient Oriented Eczema Measure			X			X	X		X	X	11.3.2.1
Dermatology Life Quality Index (DLQI)/CDLQI[7]			X			X	X		X	X	11.3.2.2
EuroQoL 5-Dimension Health Questionnaire 5-Level[8]			X			X	X		X	X	11.3.2.3
Worst Weekly Pruritus numeric rating scale[9] Eczema-related Sleep numeric rating scale[9] Patient use of topical treatment[10]	X	X	X	X	X	X	X		X	X	11.3.2.4

1) Subjects who withdraw from the trial will be followed up as described in Section 10. The final safety follow-up visit will be 16 weeks after the last dose (i.e. 14 weeks after the EOT visit).
2) The number of weeks until the EOT visit (2 weeks after the last dose of tralokinumab, maximum 140 weeks) and SFU visit (maximum 154 weeks) for each subject will depend on the time of their trial entry and treatment duration.
3) Assessments and procedures to be performed at an unscheduled visit are at the discretion of the investigator. If the unscheduled visit involves administration of rescue treatment, the investigator should make every attempt to conduct efficacy and safety assessments (at least disease severity scores [IGA and EASI], concomitant medications/procedures, and AEs) immediately before administering any rescue treatment (see Section 9.5).
4) 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.

5) At trial visits, tralokinumab will be injected at the trial site, preferably by the subject or their caregiver, alternatively by site staff. At each trial visit, subjects will be provided with tralokinumab to be administered at home until the next trial visit. In case of intercurrent illness that may compromise the safety of the subject, or fever within 72 hours prior to administration, tralokinumab administration should be rescheduled. If an anaphylactic reaction occurs, blood samples should be drawn for the analysis of serum tryptase (see details in Section 9.2).
6) 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 (leucocytes, erythrocytes, and casts) (Section 11.4.5).
7) Adult subjects from all parent trials, except the LP0162-1334 trial, will perform the DLQI. Subjects from the parent trial LP0162-1334 will perform the CDLQI, independent of the age of the subject during participation in ECZTEND.
8) Subjects from the parent trial LP0162-1334 will not perform the EuroQoL 5-Dimension Health Questionnaire 5-Level.
9) Subjects from the parent trial LP0162-1334 will perform an adolescent's pruritis NRS with a recall period of past 7 days, and an eczema-related sleep NRS with a recall period over the past 7 nights, independent of the age of the subject during participation in ECZTEND.
10) Based on subject recall during the last week prior to each site visit (from 6 days prior to each visit and including the day of the visit).

Abbreviations: CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EOT = end of treatment, 2 weeks after the last dose of tralokinumab; NRS = numeric rating scale; SFU = safety follow-up.

4.2 ECZTEND - schedule of trial procedures after May 2021

Panel 5: ECZTEND – schedule of trial procedures for subjects who re-consent/consent to participate in the trial after May 2021

	Scree-ning[1]	Treatment period[1]										EOT visit	SFU[1]	Un-scheduled visit (if applicable)[3]	Early termination (if applicable)[1]	Refe-rences (protocol section)
Weeks since first treatment in LP0162-1337	**-2**	**0**	**2**	**4**	**8**	**16**	**24**	**32 64 96 128 160 192 224 256**	**40 72 104 136 168 200 232 264**	**48 80 112 144 176 208 240**	**56 88 120 152 184 216 248**	**Variable[2] (max 268)**	**SFU visit Variable[2]**			
Visit type	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Tele-phone[4]**	**Short Site**	**Tele-phone[4]**	**Standard Site**	**Site**	**Site**			
Visit window (days)[5]	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Trial population and eligibility																
Informed consent[6]	X															Appendix 3B
Subject eligibility	X	X														8.1; 8.2, 8.3
Investigator assessments at screening/baseline only																
Demographics	X															11.2.1
Medical history	X	X														11.2.2
Height		X														11.2.3
Columbia-Suicide Severity Rating Scale	X															11.2.4

	Scree-ning[1]	Treatment period[1]										EOT visit	SFU[1]	Un-scheduled visit (if applicable)[3]	Early termination (if applicable)[1]	Refe-rences (protocol section)
Weeks since first treatment in LP0162-1337	**-2**	**0**	**2**	**4**	**8**	**16**	**24**	**32 64 96 128 160 192 224 256**	**40 72 104 136 168 200 232 264**	**48 80 112 144 176 208 240**	**56 88 120 152 184 216 248**	**Variable[2] (max 268)**	**SFU visit Variable[2]**			
Visit type	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Tele-phone[4]**	**Short Site**	**Tele-phone[4]**	**Standard Site**	**Site**	**Site**			
Visit window (days)[5]	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Treatments																
Concomitant medication and concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	9.6
Initiation of emollient[7]	X															9.4
Tralokinumab administration/ dispensing[8]		X[9]	X[9]	X[9]	X	X	X		X		X			X		9.2, 9.8.3
Treatment compliance		X	X	X	X	X	X	X	X	X	X	X		X	X	9.8.4
Investigator assessments of efficacy																
Investigator's Global Assessment		X	X	X	X	X	X		X		X	X		X	X	11.3.1.1
Eczema Area and Severity Index		X	X	X	X	X	X		X		X	X		X	X	11.3.1.2
SCORing Atopic Dermatitis		X	X	X	X	X	X		X		X	X		X	X	11.3.1.3

	Scree-ning[1]	Treatment period[1]										EOT visit	SFU[1]	Un-scheduled visit (if applicable)[3]	Early termination (if applicable)[1]	Refe-rences (protocol section)
Weeks since first treatment in LP0162-1337	**-2**	**0**	**2**	**4**	**8**	**16**	**24**	**32 64 96 128 160 192 224 256**	**40 72 104 136 168 200 232 264**	**48 80 112 144 176 208 240**	**56 88 120 152 184 216 248**	**Variable[2] (max 268)**	**SFU visit Variable[2]**			
Visit type	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Tele-phone[4]**	**Short Site**	**Tele-phone[4]**	**Standard Site**	**Site**	**Site**			
Visit window (days)[5]	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Investigator assessments of safety																
Weight		X									X	X			X	11.4.1
Vital signs	X	X	X	X	X	X			X		X	X	X	X	X	11.4.2
Physical examination	X	X			X	X			X		X	X	X	X	X	11.4.3
Electrocardio-gram	X	X				X					X	X	X	X	X	11.4.4
Hepatitis B/C, HIV	X															11.4.5
Chemistry, haematology, immunoglo-bulin E	X[10]	X			X	X					X	X	X	X	X	11.4.5
Serum pregnancy test	X															11.4.5
Urine dip stick (Urinalysis)[11]	X	X			X						X	X		X	X	11.4.5
Urine pregnancy test		X		X	X	X	X	X	X	X	X	X	X	X	X	11.4.5
Anti-drug antibodies		X		X		X					X	X	X	X	X	11.4.6

	Scree-ning[1]	Treatment period[1]										EOT visit	SFU[1]	Un-scheduled visit (if applicable)[3]	Early termination (if applicable)[1]	Refe-rences (protocol section)
Weeks since first treatment in LP0162-1337	**-2**	**0**	**2**	**4**	**8**	**16**	**24**	**32 64 96 128 160 192 224 256**	**40 72 104 136 168 200 232 264**	**48 80 112 144 176 208 240**	**56 88 120 152 184 216 248**	**Variable[2] (max 268)**	**SFU visit Variable[2]**			
Visit type	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Tele-phone[4]**	**Short Site**	**Tele-phone[4]**	**Standard Site**	**Site**	**Site**			
Visit window (days)[5]	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Investigator assessments of safety (continued)																
Pharmacoki-netics blood sample		X		X		X					X	X	X	X	X	11.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	13
Patient-reported outcomes																
Patient Oriented Eczema Measure		X				X			X		X	X		X	X	11.3.2.1
Dermatology Life Quality Index (DLQI)/ CDLQI[12]		X				X			X		X	X		X	X	11.3.2.2
EuroQoL 5-Dimension Health Questionnaire 5-Level[13]		X				X			X		X	X		X	X	11.3.2.3

	Scree-ning[1]	Treatment period[1]										EOT visit	SFU[1]	Un-scheduled visit (if applicable)[3]	Early termination (if applicable)[1]	Refe-rences (protocol section)
Weeks since first treatment in LP0162-1337	**-2**	**0**	**2**	**4**	**8**	**16**	**24**	**32 64 96 128 160 192 224 256**	**40 72 104 136 168 200 232 264**	**48 80 112 144 176 208 240**	**56 88 120 152 184 216 248**	**Variable[2] (max 268)**	**SFU visit Variable[2]**			
Visit type	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Tele-phone[4]**	**Short Site**	**Tele-phone[4]**	**Standard Site**	**Site**	**Site**			
Visit window (days)[5]	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Patient-reported outcomes (continued)																
Worst Weekly Pruritus numeric rating scale Eczema-related Sleep numeric rating scale Patient use of topical treatment[14]	X	X	X	X	X	X	X		X		X	X		X	X	11.3.2.4

1) If screening/baseline visits are performed on the same day as visit(s) in the parent trial, the order of assessments should be adhered to, working in parallel for both protocols. Assessments where data are captured in different vendor systems databases (ECG, ePRO, and laboratory tests) need to be completed twice. In such cases, the parent trial assessment should be performed first, followed by the trial LP0162-1337 assessment. For subjects included in the trial prior to protocol version 10, the first visit after May 2021 can be a site visit or a telephone visit.
2) Subjects who withdraw from the trial will be followed up as described in Section 10. The final safety follow-up visit will be 4 weeks after the last dose (i.e. 2 weeks after the EOT visit). For subjects from the parent trial LP0162-1334, the maximum number of weeks until the EOT visit will be 114 weeks.
3) Assessments and procedures to be performed at an unscheduled visit are at the discretion of the investigator. If the unscheduled visit involves administration of rescue treatment, the investigator should make every attempt to conduct efficacy and safety assessments (at least disease severity scores [IGA and EASI], concomitant medications/procedures, and AEs) immediately before administering any rescue treatment (see Section 9.5).

4) For subjects from the parent trial LP0162-1334, the telephone visit should preferably be performed as a video call.
5) If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to baseline.
6) The informed consent form must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations.
7) All subjects must use an emollient, as background treatment, twice daily (or more, as needed) for at least 14 days before baseline and must continue this treatment throughout the trial (including safety follow-up).
8) At trial visits, tralokinumab will be injected at the trial site, preferably by the subject or their caregiver, alternatively by site staff. At each trial visit from Week 4 onwards, subjects will be provided with tralokinumab to be administered at home until the next trial visit. In case of intercurrent illness that may compromise the safety of the subject, or fever within 72 hours prior to administration, tralokinumab administration should be rescheduled. If an anaphylactic reaction occurs, blood samples should be drawn for the analysis of serum tryptase (see details in Section 9.2).
9) At the first 3 tralokinumab dosing visits, subjects (or their caregiver) will be trained in how to inject tralokinumab, except for those who have already been trained in home use during the parent trial. In addition, if the subject and/or the caregiver is/are health care professional(s), no training is required, but the subject should be trained in how to handle the IMP according to the IMP handling manual and in the procedures to be followed in the event of an emergency. At the first 3 dosing visits, subjects (except for those who have received open-label tralokinumab treatment in the parent trial) will also be monitored for immediate drug reactions for a minimum of 30 minutes after dosing, with vital signs taken after 30 minutes or until stable, whichever is later.
10) IgE will not be measured at screening.
11) Urine samples will be tested with a dipstick at the trial site. A urine sample will be sent to the central laboratory for further analysis only if considered required by the investigator based on the dipstick results (Section 11.4.5).
12) Adult subjects from all parent trials, except the LP0162-1334 trial, will perform the DLQI. Subjects from the parent trial LP0162-1334 will perform the CDLQI, independent of the age of the subject during participation in ECZTEND.
13) Subjects from the parent trial LP0162-1334 will not perform the EuroQoL 5-Dimension Health Questionnaire 5-Level.
14) Based on subject recall during the last week prior to each site visit (from 6 days prior to each visit and including the day of the visit).

Abbreviations: AE = adverse event; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EOT = end of treatment, 2 weeks after the last dose of tralokinumab; IGA = Investigator's Global Assessment; IgE = immunoglobulin E; IMP = investigational medicinal product; NA = not applicable; SFU = safety follow-up.

5 Introduction and trial rationale

5.1 Atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease that may affect up to 20% of children and up to 10% of adults. In its severe form, AD is characterised by widespread skin lesions, intractable itch, as well as increased susceptibility to bacterial, viral, and fungal skin infections (Bieber 2008, Hanifin and Reed 2007, Silverberg and Hanifin 2013, Weidinger and Novak 2016). AD is associated with a substantial patient burden that typically includes poor quality of life, sleep disturbance (Jeon et al. 2017), and reductions in work productivity (Kiebert et al. 2002).

AD is characterised by an activated T-helper-2 (Th2) pathway with increased skin expression of key Th2 cytokines including interleukin (IL) 13 (Omori-Miyake et al. 2014, Tazawa et al. 2004). The expression of IL-13 is increased in lesional skin compared with non-lesional skin, and the proportion of $CD4^+$ and $CD8^+$ cells expressing IL-13 is upregulated in patients with AD compared with individuals without AD (Aleksza et al. 2002, Tazawa et al. 2004).

IL-13 acts on keratinocytes to release C-C motif chemokine ligand 22 (CCL22) and recruit more IL-13 expressing Th2 cells, decrease differentiation, and contribute to decreased barrier function (Purwar et al. 2006). IL-13 also drives immunoglobulin E (IgE) production and contributes to mast cell activation status and, once allergen cross-links IgE on the cell surface, drives histamine release and induces itch (Oh et al. 2013, Zheng et al. 2009). Indeed, itch is a key issue in AD, which drives significant mechanical damage to the skin and further facilitates allergen and pathogen entry.

These effects together drive and exacerbate the disease phenotype. A review of the available preclinical literature from mouse and human ex vivo models suggests IL-13 as a, if not the, central mediator of the AD skin phenotype. Indeed, there is evidence that blocking the IL-4 receptor (which is part of the receptor complex that also binds IL-13) with the monoclonal antibody dupilumab leads to clinical improvement in subjects with AD (Simpson et al. 2016).

5.2 Experience with investigational medicinal product

Tralokinumab is a human recombinant monoclonal antibody of the immunoglobulin G4 (IgG4) subclass that specifically binds to human IL-13 and blocks interaction with the IL-13 receptors (Blanchard et al. 2005, May et al. 2012, Thom et al. 2012).

The AD development programme investigates tralokinumab in subjects with moderate-to-severe AD. To date, 9 clinical trials have been completed: a phase 2b

dose-finding trial (trial D2213C00001), 2 phase 3 trials with tralokinumab as monotherapy (LP0162-1325 and LP0162-1326), a phase 3 trial with tralokinumab in combination with TCS (LP0162-1339), a phase 2 vaccine response trial (LP0162-1341), a phase 3 trial in adolescent subjects (LP0162-1334), a phase 1 drug-drug interaction trial (LP0162-1342), a phase 3 trial in adult subjects with severe AD ineligible to treatment with cyclosporin A (LP0162-1346), and a phase 3 trial with tralokinumab in combination with TCS (LP062-1343) in Japanese subjects with moderate-to-severe AD who are candidates for systemic therapy.

Based on the results from the dose-finding trial, the dose of 300 mg tralokinumab was chosen for the phase 3 programme.

In the pivotal phase 3 trials (LP0162-1325, -1326, and -1339), IGA, EASI, Pruritus NRS, SCORAD, and DLQI were included as the main assessments supporting the multiplicity-adjusted primary and secondary efficacy endpoints. The efficacy of tralokinumab as monotherapy in subjects with moderate-to-severe AD was demonstrated in the replicate confirmatory phase 3 trials (LP0162-1325 and LP0162-1326) with statistically significant results for all primary and multiplicity-adjusted secondary endpoints at Week 16. Likewise, the efficacy of tralokinumab in combination with TCS was consistently demonstrated by statistically significant results on all primary and multiplicity-adjusted secondary endpoints at Week 16 in the phase 3 trial LP0162-1339. Non-inferiority of tralokinumab versus placebo with respect to immune responses to concomitantly administered, non-live vaccines was demonstrated in the LP0162-1341 trial.

A total of 4,713 subjects across indications (healthy subjects, and subjects with AD, asthma, UC, and IPF) have been exposed to tralokinumab in 26 completed clinical trials, including 2,524 subjects with AD in 9 completed clinical trials. A total of 2,088 subjects with AD received tralokinumab 300 mg, and 1026 of these were exposed to tralokinumab for 52 weeks.

The safety data supports that tralokinumab was well-tolerated with a favorable safety profile when used as a monotherapy or in combination with TCS in subjects with moderate-to-severe AD who are candidates for systemic therapy. The overall frequency of SAEs was lower for tralokinumab compared with placebo, and the frequencies of AEs leading to permanent discontinuation of treatment were low and similar for the 2 treatment groups. Overall, AEs were mild or moderate in severity, and transient in nature. Furthermore, tralokinumab was well-tolerated across all evaluated subgroups, and the safety profile with self-administration of tralokinumab at home was similar to that observed after administration of tralokinumab at the site by trial site staff.

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

5.3 Trial rationale

The purpose of this trial is to evaluate the long-term safety of tralokinumab in adult and adolescent subjects as well as to evaluate the continuous response, re-treatment response, and response in tralokinumab-naïve subjects treated with tralokinumab.

Subjects eligible for this trial will have received trial treatment and completed the treatment period(s) in one of the 'parent trials': LP0162-1325, -1326, -1334, -1339, -1341, -1342, -1343, -1346, or the investigator-initiated trial TRA-WEI-0015-I (see inclusion criterion no. 2).

Subjects transferring from a blinded parent trial will enter the extension trial without their individual treatment allocation in the parent trial being unblinded. It is assumed that the majority of the subjects entering into this trial will have received tralokinumab in the parent trial – and will in the investigator's opinion have gained therapeutic benefit from tralokinumab.

Optional use of TCS is included in this trial, as subjects transferring from trials LP0162-1339, -1343, and -1346, and the open-label arms of trials LP0162-1325 -1326, and -1334 will have had this option during their treatment in the parent trial. Furthermore, the intended commercial use of tralokinumab is with or without concurrent use of TCS.

5.4 Justification for dose

The tralokinumab dosing regimen selected for this long-term extension trial is based on the dosing regimen used in the earlier trials in the tralokinumab phase 3 development programme, which in turn is based on the results of the phase 2b trial (D2213C00001) in subjects with moderate-to-severe AD.

The dose is 300 mg administered subcutaneously (SC) Q2W. Subjects from all parent trials, except the parent trial LP0162-1334, will get an initial loading dose of 600 mg tralokinumab. The administration of the loading dose will allow systemic concentrations to reach steady state faster and potentially reduce the time to onset of clinical effect, which is considered particularly important in those subjects who are tralokinumab-naïve or may have gone without tralokinumab for several weeks since their last treatment in the parent trial.

The subjects who will reach the highest exposure of tralokinumab after an initial loading dose of 600 mg tralokinumab are those who already have steady-state systemic concentrations when entering the trial, that is, subjects who have transferred directly from treatment with tralokinumab in one of the parent trials. The serum concentrations of tralokinumab after a 600 mg loading dose on top of 300 mg steady state exposure will be lower than the serum concentrations at steady state after 600 mg Q2W. A tralokinumab dosing regimen of 600 mg Q2W for up to 12 weeks was safe and well-tolerated in a phase 2a trial in adult subjects with asthma.

Subjects from the parent trial LP0162-1334, independent of the subject's age when included in ECZTEND, will not receive an initial loading dose of 600 mg tralokinumab at baseline. Based on the LP0162-1334 trial design, it is anticipated that most of the subjects have been treated with 300 mg tralokinumab Q2W prior to inclusion in ECZTEND. As there are no safety data available for the administration of a loading dose of 600 mg tralokinumab to adolescent subjects who are already at steady-state after treatment with 300 mg tralokinumab Q2W, these subjects should not be unnecessarily exposed to an initial loading dose of 600 mg tralokinumab. To maintain the blinding of the parent trial LP0162-1334, all subjects transferring from this trial will be treated with 300 mg tralokinumab Q2W. Consequently, subjects who have received 150 mg tralokinumab, 300 mg tralokinumab Q4W or placebo in the parent trial LP0162-1334, will reach the 300 mg tralokinumab Q2W steady state 2–4 weeks later than subjects who are already at steady state after treatment with 300 mg tralokinumab Q2W when included in ECZTEND.

In subjects who have had a pause in treatment with tralokinumab since their last dose in the parent trial, the exposure will be lower.

5.5 Ethical considerations

Participation in this long-term trial is voluntary and subjects can withdraw at any time. The subjects or their legally authorised representative(s) will give informed consent, and adolescent subjects will give informed assent (as appropriate and according to national laws and regulations). No vulnerable subject incapable of giving informed consent will be included in this clinical trial. Furthermore, female subjects who are pregnant, breastfeeding, or trying to become pregnant will not be included. Female subjects of childbearing potential who are sexually active, must agree to use a highly effective method of contraception to prevent pregnancy during the clinical trial and until 16 weeks after discontinuation of treatment with the investigational medicinal product (IMP). In addition, all female subjects of childbearing

potential will have a pregnancy test performed before, during, and at end of treatment to ensure that no foetuses are exposed to the IMP.

In this trial, all subjects will be treated with open-label tralokinumab with optional use of TCS or TCI. All subjects have previously participated in one of the parent trials, and the subjects who have received tralokinumab in these trials are likely to have gained a certain degree of benefit since they have agreed to participate in a long-term extension trial. Subjects will be under supervision by a dermatologist or allergist at least every 8 weeks during the treatment period until end of May 2021. For subjects who re-consent/consent to participate in the trial after May 2021, supervision by a dermatologist or allergist occurs at least every 16 weeks after May 2021 and for the remaining treatment period to reflect standard clinical practice. Between site visits, a telephone visit is mandatory to secure sufficient safety reporting. Furthermore, subjects may receive rescue therapy at the discretion of the investigator if medically necessary through treatment and follow-up. Stopping rules are specified for this trial to ensure that subjects are not continuing in a trial where they experience no benefit or where their safety is not ensured.

Altogether, the risks associated with participating in this clinical trial are considered low and outweighed by the potential treatment benefit for each participating subject as well as the benefit of a potential future treatment option for moderate-to-severe AD.

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

In conclusion, the trial design chosen for this long-term safety 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 because current immunosuppressive medications, such as cyclosporine, methotrexate, and azathioprine, are associated with long-term toxicities. Based on the benefits in treating AD reported with dupilumab, there is a reasonable expectation that tralokinumab will prove to be an effective treatment of moderate-to-severe AD. Although dupilumab exhibits an acceptable benefit/risk profile in clinical trials in AD, the long-term efficacy and safety experience with dupilumab is currently limited.

Tralokinumab has already demonstrated efficacy in moderate-to-severe AD in a phase 2b trial in adult subjects, and the evidence discussed in Section 5.2 further supports the hypothesis that adult and adolescent subjects with AD may benefit from treatment with tralokinumab. An important aspect in the benefit/risk evaluation is the reassuring safety profile of tralokinumab in AD, asthma, ulcerative colitis, idiopathic pulmonary fibrosis, and in trials with healthy subjects.

In the clinical trials completed to date, tralokinumab was well-tolerated. A number of theoretical potential risks have been identified, 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 site visits at least every 16 weeks (every 8 weeks until end of May 2021). Mandatory telephone visits will be performed between site visits to secure sufficient safety reporting after May 2021; for subjects from the parent trial LP0162-1334, this should preferably be a video call (see Panel 2 and Section 4).
- Close monitoring of subjects* after the first 3 administrations of IMP as a precautionary measure against hypersensitivity reactions (further details are given in Section 9.2).
- * Except for subjects transferring from the open-label trials LP0162-1342 and TRA-WEI-0015-I, and from the open-label tralokinumab arms of trials LP0162-1325, -1326, and -1334, all of whom are certain to have received tralokinumab.
- Monitoring of subjects for clinical manifestations that may be associated with the development of specific antibodies to tralokinumab (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) (Bancroft et al. 2000).
- Exclusion of subjects with a history of tuberculosis requiring treatment within 12 months prior to the screening visit.
- Exclusion of subjects with a history of a clinically significant infection (defined as a systemic or serious skin infection requiring parenteral antibiotics, antiviral, or anti-fungal medication; see Section 8.3) within 4 weeks prior to baseline which, in the opinion of the investigator or sponsor's medical expert, may compromise the safety of the subject in the trial.

In conclusion, previous clinical experience with tralokinumab shows no major safety or tolerability concerns, and appropriate measures have been instituted in this trial to protect subjects from potential risks that have been previously identified and to sufficiently monitor each subject. The current risk/benefit profile is considered favourable and supports the administration of tralokinumab with or without TCS therapy for the purposes of achieving the objectives of this trial.

The current COVID-19 pandemic may warrant many subjects in the ECZTEND trial to stay at home to comply with authority-issued preventive measures, which may impact subjects' ability to attend visits at the trial site. To follow authorities' restrictions and to safeguard the subjects in the ECZTEND trial as well as providing continued therapy to secure the scientific integrity, the clinical trial protocol provides an opportunity for telephone visits and courier delivery of IMP and pregnancy tests to subjects in replacement of the site visits (see Appendix 3K for details).

6 Trial objectives and endpoints

Panel 6: Objectives and endpoints

Objectives	Endpoints
Primary objective	Primary endpoint
To evaluate the long-term safety of tralokinumab	• Number of adverse events during the treatment period from baseline up to Week 268
Secondary objectives	Secondary endpoints
To evaluate the efficacy of tralokinumab given as continuous treatment, re-treatment, or introduced for the first time in tralokinumab-naïve subjects	• IGA score of 0 (clear) or 1 (almost clear) at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 • EASI75[1] at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248
	Other endpoints
	• Change in EASI score from baseline[2] to Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 • Change in SCORAD from baseline[2] to Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 • Change in POEM score from baseline[2,3] to Weeks 16, 56, 80-88, 104, 128-136, 152, 184, 216, and 248 • Change in DLQI/CDLQI[4] score from baseline[2,3] to Weeks 16, 56, 80-88, 104, 128-136, 152, 184, 216, and 248 • Change in EQ-5D-5L score from baseline[2,3,5] to Weeks 16, 56, 80-88, 104, 128-136, 152, 184, 216, and 248 • Presence of anti-drug antibodies (yes/no) • Time from first dose to permanent discontinuation of tralokinumab • Proportion of time with EASI75[1] after first occurrence of EASI75 during treatment • Proportion of time with EASI50[1] after first occurrence of EASI50 during treatment • Proportion of time with IGA 0/1 after first occurrence of IGA 0/1 during treatment • Worst Weekly Pruritus NRS at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 • Eczema-related Weekly Sleep NRS at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 • Use of topical treatment during the last week at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248

[1] EASI75 and EASI50 calculated based on baseline EASI score in parent trial. Endpoint not applicable for subjects from the parent trial TRA-WEI-0015-I, as data from the parent trial will not be transferred to LEO Pharma.

[2] 'Change from baseline' defined as change from baseline in parent trial. Endpoints not applicable for subjects from the parent trial TRA-WEI-0015-I, as data from the parent trial will not be transferred to LEO Pharma.

[3] Endpoint not applicable for subjects from the parent trial LP0162-1342, as these subjects will not have had POEM, DLQI/CDLQI, or EQ-5D-5L assessments in the parent trial, and thus are missing baseline assessments.

[4] All subjects from the parent trial LP0162-1334, independent of the subject's age during participation in ECZTEND, will perform the Children's Dermatology Life Quality Index (CDLQI), an adolescent's pruritis NRS with a recall period of past 7 days, and an eczema-related sleep NRS with a recall period over the past 7 nights (see rationale in Section 12).

[5] Endpoint not applicable for subjects from the parent trials LP0162-1334, and -1343, as these subjects will not have had EQ-5D-5L assessments in the parent trial and thus are missing the baseline assessment. In addition, the EQ-5D-5L questionnaire has not been validated for adolescents.

Abbreviations: CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI75/EASI50 = at least 75% / 50% reduction in EASI score, relative to baseline in parent trial; EQ-5D-5L = EuroQoL 5-Dimension Health Questionnaire 5-Level; IGA = Investigator's Global Assessment; NRS = numeric rating scale; POEM = Patient Oriented Eczema Measure; SCORAD = Scoring Atopic Dermatitis.

7 Trial design

7.1 Overall trial design

7.1.1 Overview

This is an open-label phase 3 trial to study the long-term safety of tralokinumab administered to adult subjects (≥18 years) and adolescent subjects (12 to <18 years) with AD who participated in previous trials with tralokinumab. The trial will include a screening period of 2 weeks (Week -2 to Week 0), which is expected to overlap with the last period in the parent trial for the majority of subjects, and a long-term treatment period of approximately 0.5 years to up to 5 years. The duration of the treatment period for each subject will depend on when they enter the trial after completing the parent trial, and by which treatment stop date they have consented to (end of May 2021, end of May 2022, or a country-specific end of treatment day according to Appendix 3J).

The visit schedule until May 2021 is different from the visit schedule after May 2021, where a number of site visits were replaced by mandatory telephone visits to reduce the burden of frequent site visits (Panel 2 and Panel 5).

7.1.1.1 COVID-19 pandemic guidance

In the case where a subject is unable to attend site visits due to the COVID-19 pandemic, please refer to Appendix 3K for guidance.

7.1.2 Screening period (Week -2 to Week 0)

Prior to attending any trial procedure, a signed informed consent must be obtained from the subject or the adolescent subject's legally authorised representative(s), and a signed informed assent must be obtained from the adolescent subject (as appropriate and according to national laws and regulations).

To avoid a gap between the parent trial and extension trial, screening should ideally start before the end of the parent trial. Hence, the screening period is expected to overlap with the last period in the parent trial for the majority of subjects: the last visit in the parent trial could ideally coincide with the baseline visit of the extension trial. However, subjects can be included in the ECZTEND trial up to 26 weeks after the last IMP dose in the parent trial.

To avoid duplicate reporting of AEs, any AE with onset before the final visit in the parent trial should be reported as an AE in the parent trial. If ongoing, the AE should also be recorded as medical history in the current extension trial (see Section 11.2.2). AEs with onset after the

final visit in the parent trial and after informed consent has been obtained for the extension trial should be recorded as an AE in the extension trial.

The screening period has a duration of 2 weeks. Eligibility will be assessed at the screening visit and at baseline prior to start of treatment. Should the screening exceed a duration of 2 weeks, the sponsor should be consulted, and approval sought before the subject can attend Visit 3 (baseline visit).

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

7.1.3 Treatment period (Week 0 and onwards)

7.1.3.1 Treatment initiation

Following the screening period, and at least 2 weeks after the last dose in the parent trial, subjects from all parent trials except the parent trial LP0162-1334, will receive an initial loading dose of 600 mg tralokinumab (4 mL) at baseline. Subjects from the parent trial LP0162-1334 will start with a dose of 300 mg tralokinumab (2 mL) at baseline. For the rest of the treatment period, all subjects will receive a dose of 300 mg tralokinumab Q2W (2 mL). Tralokinumab will be administered by subcutaneous (SC) injection.

Subjects will self-inject tralokinumab – or have tralokinumab injected by a caregiver – in their home after adequate training by site staff during the 3 first treatment visits (Weeks 0, 2, and 4). Subjects who already have experience with home use of tralokinumab from participation in open-label arms of trials LP0162-1325, -1326, and -1334 can start self-injecting at baseline without training (see also Section 9.2). At the trial visits, tralokinumab will be injected at the trial site, preferably by the subject or their caregiver, alternatively by site staff.

The first 3 treatment visits will also be used for post-dose monitoring for immediate drug reactions (see Section 9.2), as some subjects will have received placebo in the parent trial and are thus naïve to tralokinumab. Subjects who have transferred from the open-label trials LP0162-1342 or TRA-WEI-0015-I, or the open-label arms of trials LP0162-1325, -1326, or -1334, and who have received at least 3 doses of tralokinumab in the parent trial will not need to be observed.

Subjects can use TCS (US class ≥4 or Europe class ≤3) or TCI at the investigator's discretion. If TCS are used, the subject should be monitored for signs of local or systemic TCS toxicity, and the safety and appropriateness of continued or repeated courses of TCS therapy should be evaluated by site staff.

Treatment is described in more detail in Section 9.

7.1.3.2 Treatment period until end of May 2021 (all subjects)

All subjects included in the trial prior to protocol version 10, attended site visits every 8 weeks until the last visit before end of May 2021, and followed the schedules of trial procedures in Section 4.1.

At end of May 2021, the procedures applicable depended on whether the subjects did NOT or DID accept to continue in the trial after May 2021:

- **Subject did NOT re-consent to continue in the trial after May 2021:**
  The subject continued to follow the trial procedures in Section 4.1. The subject had to be supplied with IMP for home dosing until end of May 2021, where treatment had to be stopped.
- **Subject DID re-consent to continue in the trial after May 2021:**
  After signing the consent form (subject or legal authorised representative), as well as the assent form for adolescent subjects, the last visit before end of May 2021 had to be completed as a normal site visit (i.e. not as an EOT visit). After that, the schedule of trial procedures in Section 4.2 was followed (see description of treatment period after May 2021 in Section 7.1.3.3).

7.1.3.3 Treatment period after May 2021

Subjects who wanted to participate in the trial after May 2021 had to re-consent (subjects included based on earlier protocol versions than version 10) or consent (subjects included based on protocol versions 10 to 12) to participate.

Subjects who re-consented/consented to participate in the trial after May 2021 follow the modified schedule of trial procedures specified in Section 4.2:

- For subjects included in the trial based on protocol versions 10 to 13, treatment will be initiated as described in Section 7.1.3.1.

- For subjects included in the trial prior to protocol version 10, the first visit after May 2021 can be a site visit or a telephone visit. The first site visit may be after 8 weeks before starting the 16-week schedule to align individual visit schedules with endpoints.
- All subjects who re-consented/consented to participate in the trial after May 2021: subjects will start with a 24-week period with more frequent visits, and then continue with site visits (standard site visits or short site visits) every 16 weeks, interchanging with a telephone visit in between the site visits. For subjects from the parent trial LP0162-1334, the telephone visit should preferably be a video call. Visit types during the treatment period are described in Section 7.1.3.4.
- Treatment completion dates are dependent on the subject's consent and are done according to Panel 7.

Panel 7 Treatment completion date

Parent trial	Subject did NOT consent to continue after May 2021	Subject DID re-consent or consent to participate after May 2021
LP0162-1325, -1326, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I	End of May 2021	Country-specific end date according to Appendix 3J
LP0162-1334 (adolescents)	End of May 2021	End of May 2022

7.1.3.4 Trial visits in the treatment period

Site visits until end of May 2021

Until end of May 2021, all subjects included in the trial prior to protocol version 10, attended site visits every 8 weeks. At each site visit, subject or subject's caregiver (or investigator) administered tralokinumab and assessed concomitant medications and treatment compliance. The following assessments were performed according to the trial procedures specified in Section 4.1:

- Efficacy assessments: IGA, EASI, and SCORAD.
- Safety assessments: weight, vital signs, physical examination, ECG, laboratory parameters (chemistry, haematology and immunoglobulin E), urinalysis, urine pregnancy test (if applicable), anti-drug antibodies (ADA), pharmacokinetics (PK), and AEs.
- Patient-reported outcomes: POEM, DLQI/CDLQI, EQ-5D-5L*, eczema-related sleep NRS, worst weekly pruritus NRS/adolescent's pruritis NRS, and patient use of topical treatment.

- *The EQ-5D-5L is not performed by subjects from the parent trial LP0162-1334.

Details of assessments are described in Section 11.

Visits after May 2021

After May 2021, subjects who re-consented to continue or consent to be included in the trial after May 2021, will attend 2 types of site visits (standard site visits and short site visits), interchanging with a telephone visit in between the site visits, according to the trial procedures presented in Section 4.2. The 3 types of visits are described below.

Standard site visit

At each standard site visit (Weeks 56, 88, 120, 152, 184, 216, and 248), subject or subject's caregiver (or investigator) will administer tralokinumab and assess concomitant medications and treatment compliance. In addition, the following assessments will be performed:

- Efficacy assessments: IGA, EASI, and SCORAD.
- Safety assessments: Weight, vital signs, physical examination, ECG, laboratory parameters (chemistry, haematology and immunoglobulin E), urine dipstick, urine pregnancy test (if applicable), ADA, PK, and AEs.
- Patient-reported outcomes: POEM, DLQI/CDLQI, EQ-5D-5L*, eczema-related sleep NRS, worst weekly pruritus NRS/adolescent's pruritis NRS, and patient use of topical treatment.
- *The EQ-5D-5L is not performed by subjects from the parent trial LP0162-1334.

Details of assessments are described in Section 11.

Short site visit

At each short site visit (Weeks 40, 72, 104, 136, 168, 200, 232, and 264), subjects or subject's caregiver (or investigator) will administer tralokinumab and assess concomitant medications and treatment compliance. In addition, the following assessments will be performed:

- Efficacy assessments: IGA, EASI, and SCORAD.
- Safety assessments:Vital signs, physical examination, pregnancy test (if applicable), and AEs.
- Patient-reported outcomes: POEM, DLQI/CDLQI, EQ-5D-5L*, eczema-related sleep NRS, worst weekly pruritus NRS/adolescent's pruritis NRS, and patient use of topical treatment.

- *The EQ-5D-5L is not performed by subjects from the parent trial LP0162-1334.

Details of assessments are described in Section 11.

Telephone visit

Subjects will be contacted via telephone (telephone visit) 8 weeks after site visits (standard site visit or short site visit). For subjects from the parent trial LP0162-1334, this should as far as possible be a video call.

At each telephone visit, AEs, concomitant medication, treatment compliance, and pregnancy test result (if applicable) are assessed. The pregnancy test must be performed by the subject at home within 48 hours before the telephone visit, and a negative result informed to the site staff before the subject can continue treatment.

Delegation of the telephone visit to qualified personnel is allowed at the discretion of the investigator.

Details of assessments are described in Section 11.

7.1.4 Safety follow-up period (after last IMP dose)

All subjects will complete an off-treatment follow-up period for the assessment of safety, PK, and ADA.

The timing of the safety follow-up visit depends on the parent trial and on whether the subject has consented to participate after May 2021, as summarised in Panel 8.

Panel 8: Safety follow-up visit

Parent trial	Subject did NOT consent to continue after May 2021	Subject DID re-consent or consent to participate after May 2021
LP0162-1325, -1326, -1334 (adolescents), -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I	16 weeks after last dose	4 weeks after last dose

7.2 Number of subjects needed

The assumed sample size for this trial is approximately 1,600 subjects. No formal sample size has been calculated; the sample size is based on the population sizes of the parent trials and assumptions regarding how many subjects will complete the parent trials and be eligible for / consent to participate in the current extension trial.

This trial will be conducted at approximately 330 sites in Canada, Europe, Japan, and the US. The number of subjects per trial site will depend on how many of the subjects in the parent trial meet the eligibility criteria for, and choose to participate in, the extension trial.

7.3 End of trial definition

The end of the trial is defined as the date of the last visit of the last subject in the trial globally. By the end of this trial, subjects will have been exposed to tralokinumab for up to 5 years, which is considered appropriate for evaluating long-term safety of tralokinumab.

The final collection of data for the primary endpoint will occur by Q2 2024.

A subject is considered to have completed the trial if the subject has completed all periods of the trial, including the safety follow-up visit, according to protocol version 13 or earlier versions.

The duration of the treatment period for each subject will depend on when the subject enters the trial after completing the parent trial, and by which treatment stop date they have consented to (end of May 2021, end of May 2022, or a country-specific end of treatment day according to Appendix 3J). Hence, a subject is considered to have completed the treatment period for either of the following scenarios:

- Approximately end of May 2021 for subjects completing according to earlier versions than protocol version 10.
- Approximately end of May 2022 for subjects from the parent trial LP0162-1334 who consented to continue in the trial after May 2021.
- At a country-specific end of treatment date (Appendix 3J) for subjects from the parent trials LP0162-1325, -1326, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I who consented to continue in the trial after May 2021.

See Section 11.8 for the end of trial procedures.

7.4 Software

CDISC controlled terminology version 30-Mar-2018 (or newer) was used for definition of controlled terminology used throughout this protocol and will be used for statistical programming and output. Study Data Tabulation Model (SDTM) v1.4 with SDTM Implementation Guide 3.2 (or newer) 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 safety risk by participating in the trial and can be expected to comply with the protocol. It is assumed that subjects entering this trial will in the investigator's opinion have the potential to gain therapeutic benefit from treatment with tralokinumab irrespectively of whether the subject received tralokinumab or placebo in the parent trial.

The subject's eligibility for the clinical trial must be verified according to the inclusion and exclusion criteria at visits specified in Section 4. It will be recorded in the eCRF if the subject has met all the inclusion criteria and none of the exclusion criteria.

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

8.2 Inclusion criteria

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

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures. Signed and dated informed consent for adolescent subjects must be provided by the subject's legal representative(s) and by the subject in the form of a signed and dated informed assent (as applicable according to national laws or regulations).
2. Subjects must have completed* the treatment period(s) of one of the parent trials: LP0162-1325, -1326, -1334, -1339, -1341, -1342, -1343, -1346, or TRA-WEI-0015-I.
   - *To be assessed on the first day of IMP administration (baseline).
3. Subjects must have complied with the clinical trial protocol in the parent trial to the satisfaction of the investigator.
4. Subjects must be able and willing to self-administer tralokinumab treatment (or have it administered by a caregiver) at home after the initial 3 injection visits at the trial site (in this trial).
5. Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days prior to baseline.

6. Female subjects of childbearing potential (defined as Tanner stage ≥3 or menarche)* must use a highly effective** form of birth control (confirmed by the investigator) continuously for at least 1 month prior to the pregnancy test at baseline (Week 0), throughout the trial, and for at least 16 weeks (5 half-lives of the IMP) after the last administration of IMP.

   *A female subject is defined as not being of childbearing 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).
   - Premenarchal.

   **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), same-sex partner, or vasectomised partner (given that the subject is monogamous).

8.3 Exclusion criteria

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

1. Any condition that required permanent discontinuation of trial treatment in the parent trial.
2. More than 26 weeks have elapsed* since the subject received the last IMP injection in the parent trial.

   * To be assessed on the first day of IMP administration (baseline).

3. Subjects who, during their participation in the parent trial, developed a serious adverse event (SAE) deemed related to tralokinumab by the investigator, which in the opinion of the investigator could indicate that continued treatment with tralokinumab may present an unreasonable safety risk for the subject.

4. Subjects who, during their participation in the parent trial, developed an AE that was deemed related to tralokinumab by the investigator and led to temporary discontinuation of trial treatment, which in the opinion of the investigator could indicate that continued treatment with tralokinumab may present an unreasonable safety risk for the subject.
5. Receipt of any marketed biological therapy or investigational biologic agent (other than tralokinumab), including immunoglobulin, anti-IgE, or dupilumab:
    - Any cell-depleting agents, including but not limited to rituximab: within 6 months prior to baseline, or until lymphocyte count returns to normal, whichever is longer.
    - Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline.
6. Treatment with the following medications within 5 half-lives prior to baseline:
    - Systemic immunosuppressive/immunomodulating drugs (for example, methotrexate, cyclosporine, azathioprine, mycophenolate-mofetil, Janus kinase inhibitors).
    - Systemic corticosteroids (excluding topical, ophthalmic, inhaled, or intranasal delivery).
7. Treatment with topical PDE-4 inhibitors or topical JAK inhibitors within 2 weeks prior to baseline.
8. 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 are eligible provided they are vaccinated against hepatitis B and have negative HBsAg and HBcAb.

    *Subjects from the parent trial LP0162-1343 with a positive HBsAb may be assigned treatment provided they have negative HBsAg, HBcAb, and HCV serology at screening.
9. Known or suspected hypersensitivity to any component(s) of the IMP.
    - Subjects who during the parent trial have had a localised injection site reaction suspected to be due to hypersensitivity are eligible provided that the subject has been able to continue IMP administrations and there has been no sign of a systemic hypersensitivity reaction.

10. History of anaphylaxis following any biological therapy.
11. History of immune complex disease.
12. 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 when informed consent was obtained.
        - Subjects who during the parent trial 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 has been completed.
    - 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 when informed consent was obtained.
13. Tuberculosis requiring treatment within 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care.
14. 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 or subject's verbal report.
15. Current participation in any other interventional clinical trial, except for tralokinumab trials LP0162-1325, -1326, -1334, -1339, -1341, -1342, -1346, -1343, or TRA-WEI-0015-I.
16. Previously screened in this clinical trial.
17. Receipt of live attenuated vaccines 30 days prior to baseline and during the trial including the safety follow-up period.
    - Receipt of inactive/killed vaccines (for example, inactive influenza and inactive COVID-19 vaccines) is allowed, provided they are not administered within 5 days before/after any IMP injection.
18. Receipt of blood products within 4 weeks prior to baseline.
19. Major surgery within 8 weeks prior to baseline, or planned in-patient surgery or hospitalisation during the trial period.

20. History of subject or subject's legal representative(s) of chronic alcohol or drug abuse within 12 months prior to screening, or any condition (e.g., psychotic state, language barrier or other) associated with poor compliance, as judged by the investigator.
21. 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.
22. Subjects who are legally institutionalised.
23. Female subjects who are pregnant, breastfeeding, or lactating.
24. History of attempted suicide or significant risk of suicide (either in the opinion of the investigator, or defined as a "yes" to suicidal ideation questions 4 or 5, or answering "yes" to suicidal behaviour on the Columbia-Suicide Severity Rating Scale [C-SSRS] screening version).
25. History of a clinically significant infection 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, 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.
26. A helminth parasitic infection within 6 months prior to the date when informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy.
27. Any disorder that is not stable and in the opinion of the investigator could:
    - Affect the safety of the subject throughout the trial.
    - Influence the findings of the trial.
    - Impede the subject's ability to complete the trial.

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

- Influence the results of the trial.
- Influence the subject's ability to complete the trial.

The abnormal finding must be clinically significant and observed during the screening period. Examples include abnormal findings in physical examination, vital signs, electrocardiogram (ECG [based on the central ECG evaluation report]), or central laboratory results (haematology, clinical chemistry, or urinalysis).

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 unique subject identification number (subject ID) will be assigned by including the subject through the EDC system, and the screening evaluations to assess eligibility criteria may begin. The subject ID consists of 5 digits, the first 3 of which refer to the site number, the latter 2 are sequential numbers, starting from 01. The subject ID will be different from that in the parent trial, and will be used to identify the subject during the screening process and throughout trial participation, if applicable. Subjects who have given written informed consent and subjects for whom the subject's legally authorised representative(s) have given written informed consent (the subject must have given written informed assent, as appropriate and according to national laws and regulation) 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 Pharma. In addition, the investigator will maintain a log of all subjects considered for screening, whether they or their legal representative(s) have provided written informed consent (and informed assent as appropriate and according to national laws and regulation) 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 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 (Schulz 2010) and to

respond to queries from regulatory authorities. The following data will be collected in the eCRF for screening failures:

- Date of informed consent (s).
- Demographics (age, date of birth [or only year and month of birth as applicable to local legislation], sex, ethnicity, race).
- Reason for screening failure.
  - Failure to meet eligibility criteria.
  - Lost to follow-up.
  - Withdrawal by subject.
  - Withdrawal by parent/guardian.*
  - Other.
- Date of screen failure.
- Any adverse events (AEs) and serious AEs (SAEs) with onset after the final visit in the parent trial (AEs and SAEs with onset before the final visit in the parent trial should be reported as an AE in the parent trial).

*For adolescent subjects as applicable.

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

9 Treatments

9.1 Trial product description

Panel 9: Identification of investigational medicinal product (IMP)

IMP	Dosage form	Active ingredient and concentration	Pack size
Tralokinumab	Solution for injection	Nominal concentration of tralokinumab 150 mg/mL in CCI mM sodium acetate/acetic acid buffer, CCI mM sodium chloride, CCI % (w/v) PS-CCI, pH CCI	1.0 mL pre-filled accessorised syringe[1]

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

9.2 Administration of IMP

The EDC system will assign the required kit number(s) for each subject at each dispensing visit.

The first day of dosing with tralokinumab is considered baseline (Visit 3). At this visit, subjects from all parent trials except the parent trial LP0162-1334, will receive 4 SC injections (1.0 mL each) of 150 mg tralokinumab to receive a total initial loading dose of 600 mg tralokinumab. At baseline, subjects from the parent trial LP0162-1334 will receive 2 SC injections (1.0 mL each) of 150 mg tralokinumab to receive a total initial dose of 300 mg tralokinumab. For the rest of the treatment period, all subjects will receive a total dose of 300 mg tralokinumab every second week (Q2W). A minimum interval of 7 days is required between 2 dosings.

The dosing regimen is presented in Panel 10.

Panel 10: Dosing regimen

Subjects from all parent trials except the LP0162-1334 trial	Subjects from the parent trial LP0162-1334
Initial loading dose at baseline • 600 mg tralokinumab, single dose of 4 SC injections with 1 mL of 150 mg/mL tralokinumab Dose for the rest of the treatment period • 300 mg tralokinumab Q2W, 2 SC injections with 1 mL of 150 mg/mL tralokinumab every second week	Dose during the treatment period (also at baseline) • 300 mg tralokinumab Q2W, 2 SC injections with 1 mL of 150 mg/mL tralokinumab every second week

Abbreviations: Q2W = every second week; SC = subcutaneous

Subjects will self-inject tralokinumab – or have tralokinumab injected by a caregiver – in their home after adequate training by the investigator or delegated site staff during the 3 first treatment visits. In addition, if the subject and/or the caregiver is/are health care professional(s), no training is required, but the subject should be trained in how to handle the IMP according to the IMP handling manual and in the procedures to be followed in the event of an emergency. The individual who will be performing the injection (that is, the subject, caregiver, or both) will be trained in proper SC injection technique and procedures to be followed in the event of an emergency during or following home use of tralokinumab. The subject (and/or caregiver) must inject tralokinumab under supervision by the trainer on one or more occasions such that the trainer is satisfied with the individual's understanding and confidence of the procedure.

Subjects who already have experience with home use of tralokinumab from participation in open-label arms of trials LP0162-1325 or LP0162-1326 can start self-injection at baseline without training.

At trial visits, tralokinumab will be injected at the trial site, preferably by the subject or their caregiver, alternatively by site staff, when all assessments have been completed. It will be recorded in the eCRF (for trial visits only) whether tralokinumab was injected by the subject/caregiver or site staff.

Tralokinumab will be injected into the SC tissue of the upper arm, anterior thigh, or abdomen, separated by at least 3 cm within the same anatomical location. It is advised that the site of injection of IMP is rotated such that the subject receives IMP at a different anatomical part at each treatment. The injection site must be recorded in the source documents at each treatment visit and recorded in the eCRF.

Further details on IMP administration are provided in a trial product handling manual. Subjects will also receive a pamphlet with instructions for IMP self-administration. IMP must be administered according to these instructions.

IMP dosing/dispensing visits are shown in the schedule of trial procedures (Section 4).

After administration of tralokinumab

For the first 3 tralokinumab dosing visits (Weeks 0, 2, and 4), subjects will be monitored for immediate drug reactions for a minimum of 30 minutes after administration of tralokinumab, with vital signs measured after 30 minutes or until stable, whichever is later. Vital signs will be documented in the eCRF. Subjects who have participated in open-label tralokinumab arms of trials LP0162-1325, -1326, or -1334, or from one of the open-label trials LP0162-1342 and TRA-WEI-0015-I, and who have received at least 3 doses of tralokinumab in the parent trial, are exempt from this monitoring.

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) (Johansson et al. 2004). The clinical criteria for defining anaphylaxis for this trial are listed in Appendix 6 (Sampson et al. 2006). Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc., and medical equipment to treat acute anaphylactic reactions must be immediately available at the trial sites, and trial personnel should be trained to recognise and respond to anaphylaxis according to local guidelines.

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

Conditions requiring rescheduling of tralokinumab administration

If any of the following should occur, the investigator should reschedule the visit and tralokinumab 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 during the trial (for example, viral illness).
- The subject is febrile (defined as ≥38°C) within 72 hours prior to administration of tralokinumab.

If the trial visit cannot be rescheduled to maintain a minimum of 7 days before the next 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 assigned to treatment with tralokinumab at baseline.

9.4 Background treatment

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

9.5 Rescue treatment

If medically necessary (that is, 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 (higher potency TCS: US class <4 or Europe class >3) will continue treatment with IMP. If TCS are used as rescue treatment, the subject should be monitored for signs of local or systemic TCS toxicity, and the safety and appropriateness of continued use should be supervised by site staff.

If a subject receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (for example, cyclosporine, methotrexate, mycophenolate mofetil, azathioprine), treatment with IMP will be immediately discontinued (see Section 10.2.3). After the treatment with these medications is completed, IMP may be resumed if deemed appropriate by the investigator, but not sooner than 5 half-lives after the last dose of systemic rescue treatment. The use of biological rescue treatment will be disallowed for the entire trial duration.

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

9.6 Concomitant medication and concurrent procedures

Any medication (except for IMP/NIMP including momethasone furoate, CYP cocktail, and vaccine received in the treatment periods in the parent trials) that the subject receives from 3 months prior to screening through the safety follow-up, including any of the permitted concomitant medications specified below, must be recorded in the subject's medical record and the eCRF along with details such as:

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

Similarly, concurrent procedures must also be recorded in the subject's medical record and the eCRF. Note that only surgical procedures and procedures related to AD treatment (for example, phototherapy or bleach baths) should be recorded. The following details will be recorded: procedure, body location (upper limb, lower limb, trunk, head), diagnosis, and start and stop date (it will also be recorded if the procedure is ongoing).

At all site visits and telephone visits, subjects should be asked whether they have used TCS or TCI (see below) during the past week – to make it possible to assess whether the individual efficacy response is achieved with or without topical therapy and to get an impression of topical medication use.

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

The following concomitant medications related to AD treatment are permitted from screening through the safety follow-up:

- TCS (US class ≥4 or Europe class ≤3) or TCI.
- Oral antibiotics, antiviral, or antifungal therapy for skin infections as appropriate.

- Stable doses of an emollient (see Section 9.4; subjects must apply emollient twice daily [or more, as needed] for at least 14 days before baseline and throughout trial participation).
- Oral anti-histamines.

9.7 Prohibited medication and procedures

The medications below are prohibited during the trial. For specifications on allowed rescue treatment for AD symptoms, please refer to Section 9.5.

From baseline through end of treatment:

- Higher potency topical corticosteroids (US class < 4 or Europe class > 3). Can be used as rescue for intolerable AD symptoms (see Section 9.5).
- Topical phosphodiesterase 4 (PDE-4) inhibitors.
- Topical and systemic JAK inhibitors.
- UVA or UVB, psoralen + UVA (PUVA), other phototherapy, or tanning beds.
- 3 or more bleach baths per week.

From baseline through safety follow-up:

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

In case prohibited systemic medications are received, IMP dosing must be suspended as described in Section 10.2.3.

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

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

* Receipt of inactive/killed vaccines (for example, inactive influenza and inactive COVID-19) is allowed, provided they are not administered within 5 days before/after any IMP injection.

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

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

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

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

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

9.8.2 Storage of trial products

All IMP supplied by LEO Pharma must be stored in a secure and restricted area under the conditions specified on the label and remain in the original container until dispensed.

The IMP must be stored at 2–8°C at the trial site. The temperature during storage should be monitored by a calibrated, stationary, and continuously monitoring system. Minimum requirement is a calibrated min/max thermometer.

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

Storage of IMP may be delegated, for example to a hospital pharmacy, as locally applicable.

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

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

Damaged IMP should be documented in the IRT and reported as a product complaint (see Section 9.10). Damaged IMP may not be used.

Further details on IMP storage (including handling of such cases as listed above) and home use are provided in a trial product handling manual. The pamphlet given to subjects with instructions for IMP self-administration also provides instruction on IMP storage during home use.

9.8.3 Drug accountability

The investigator is fully responsible for the IMP at the trial site, for maintaining adequate control of the IMP, and for documenting all transactions with them. Dispensing of IMP may be delegated, for example to a hospital pharmacy, as locally applicable.

An individual drug accountability form (or similar) must be kept of the IMP administered to and returned by each subject in the trial. This individual drug accountability form must be available during monitoring visits and will be checked by the CRA to verify correct dispensing of the IMP. Drug accountability information will be entered in the IRT, where inventory status of all IMP at the trial site will also be maintained.

Subjects will attend site visits on a regular basis (see Section 4). At these site visits, subjects will be provided with IMP to be administered at home until the next site visit. Subjects will be provided with sharps bins for used syringes and will return filled sharps bins to the trial site. Subjects will return trial kit cartons and any unused IMP at each site visit. Unused IMP returned by subjects to the trial site can be stored at room temperature and must be stored separately from non-allocated IMP.

All unused IMP supplied by the contract manufacturing organisation (CMO) on behalf of LEO Pharma will be returned to the CMO. Prior to 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 on drug accountability forms and in the IRT.

Reporting in eCRF
IMP kit numbers and the date of IMP administration will be recorded in the eCRF. In addition, the site of IMP injection should be given. Subjects will be asked to record these details in a log (paper form) of drug administration for each IMP administration at home, and site staff will record the details in the eCRF.

9.8.4 Treatment compliance

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

Where IMP is injected by the subject or subject's caregiver at the trial site, the site staff will record compliance data in the eCRF.

Where IMP is injected by the subject or subject's caregiver at home, the subject or subject's caregiver will record the date and injection site for each administration in a log of drug

administration; these data will be transcribed into the eCRF by site staff at the next site or telephone visit. If a subject is found to be non-compliant, the investigator should remind the subject of the importance of following the treatment instructions including taking the IMP as prescribed. Any non-compliance and the reason for it must be recorded in the eCRF.

9.8.5 Trial product destruction

Used syringes will be destroyed at the trial site provided the trial site has procedures in place for such IMP destruction. Trial sites that do not have such IMP destruction procedures in place will dispose used IMP in sharps bins that will be shipped to the CMO.

Unused IMP and used syringes returned to the CMO will be destroyed by the CMO according to approved procedures and any local requirements.

9.9 Provision for subject care following trial completion

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.

9.10 Reporting product complaints

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

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

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

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

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

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

Fax number: +45 6910 2468

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

10 Discontinuation and withdrawal

10.1 General principles

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

Subjects who withdraw from the trial will not be replaced.

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

10.2 IMP discontinuation rules

10.2.1 Stopping rules

Since it is considered unethical to continue the treatment with IMP in subjects who gain no therapeutic benefit after a reasonable treatment period, subjects should permanently discontinue IMP and be withdrawn from the trial if, based on the investigator's assessment, one of the following events occurs:

- Continuous use of higher potency TCS (US class <4 or Europe class >3) for >4 weeks.
- Continuous use of systemic rescue treatment for >3 weeks.
- Disease severity above or equal to baseline in the parent trial for a duration of ≥8 weeks.

The stopping rules will be effective from Week 16.

Subjects who (in the opinion of the subject, the subject's legally authorised representative(s), or investigator) have unacceptable treatment effect of IMP may also be withdrawn from the trial at any time without fulfilling any of the stopping rules. Subjects withdrawn from the trial should complete the safety follow-up period as specified in Section 7.1.

Reasons for withdrawal from the trial are described in Section 10.2.2.

10.2.2 Reasons for withdrawal from the trial

Subjects will permanently discontinue IMP and be withdrawn from the trial 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:
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values >3×upper limit of normal (ULN) with total bilirubin >2×ULN (unless elevated bilirubin is related to Gilbert-Meulengracht Syndrome).
  - Confirmed AST or ALT >5×ULN for >2 weeks.

Subjects withdrawn from the trial must complete the safety follow-up period as specified in Section 7.1.

Data to be recorded in the eCRF

The primary reason for withdrawal from the trial must be recorded in the medical records and on the end of trial form (see Section 11.8) in the eCRF, where the following reasons are available:

- Lack of efficacy.
- Adverse event.
- Withdrawal by subject.
- Withdrawal by parent/guardian.*
- Lost to follow-up.
- Death.
- Other.

*For adolescent subjects as applicable.

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

Stopping rules are described in Section 10.2.1.

10.2.3 Reasons for temporary discontinuation of IMP

IMP dosing MAY be temporarily suspended in the event of:

- Other intercurrent illness or major surgery.
- An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents.

IMP dosing SHOULD be temporarily suspended in the event of:

- Treatment with systemic corticosteroids or non-steroidal immunosuppressive/immunomodulating medications (for example, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, Janus kinase inhibitors, dupilumab, or other biologics).

After the treatment with these medications is completed, IMP may be resumed if deemed appropriate by the investigator, but not sooner than 5 half-lives after the last dose of systemic rescue treatment. If any of the stopping rules are met (see Section 10.2.1) or any of the withdrawal reasons are met (Section 10.2.2), the subject must be withdrawn from the trial.

10.3 Early termination assessments

Withdrawal from trial

Subjects withdrawn from the trial for any reason should attend an early termination visit as soon as possible after the last administration of IMP and should return to the trial site for a safety follow-up visit after last administration of IMP as specified in Section 7.1.4. 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. An EOT (end of treatment) form and an end of trial form must be completed as specified in Section 11.8. No EOT visit is to be done for subjects who are withdrawn from 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 or subject's parent/guardian and reschedule the missed visit as soon as possible, as well as counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject or the subject's parent/guardian (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

Evaluations to be done at each site visit are shown in the schedule of trial procedures in Section 4. Refer to Section 7.1 for further details on the trial design.

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

- PROs in the following order:
    1. Patient Oriented Eczema Measure (POEM).
    2. Dermatology Life Quality Index (DLQI)/Children's Dermatology Life Quality Index (CDLQI).*
    3. EuroQoL 5-Dimension Health Questionnaire 5 Level (EQ-5D-5L)*.
    4. Eczema-related Weekly Sleep numeric rating scale (NRS).*
    5. Worst Weekly Pruritus NRS.*
    6. Patient use of topical treatment.
- *All subjects from the parent trial LP0162-1334, independent of the subject's age during participation in ECZTEND, will perform the Children's Dermatology Life Quality Index (CDLQI), an adolescent's pruritis NRS with a recall period of past 7 days, and an eczema-related sleep NRS with a recall period over the past 7 nights; these subjects will not perform the EQ-5D-5L as this questionnaire has not been validated for adolescents.
- Investigator assessments (performed only by adequately trained investigators; to reduce inter-rater variability, the same investigator should preferably perform all the evaluations for a given subject throughout the entire trial period) in the following order:
    1. SCORAD component C, then component A and B.
    2. IGA.
    3. EASI.
- Safety and laboratory assessments.
- Administration and dispensing of IMP.

If screening/baseline visits are performed on the same day as visit(s) in the parent trial the following applies:

- The order of assessments should be adhered to, working in parallel for both protocols.
- Assessments where data are captured in different vendor systems databases (ECG, ePRO, and laboratory tests) need to be completed twice. In such cases, the parent trial assessment should be performed first, followed by the trial LP0162-1337 assessment.

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

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 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).

11.2 Assessments performed only at screening/baseline

11.2.1 Demographics

The following demographic data will be recorded:

- Age and date of birth (or only year and month of birth as applicable to local legislation).
- Sex.
- Race: American Indian or Alaska native, Asian, black or African American, native Hawaiian or other Pacific islander, white, other.
- Ethnic origin (self-reported by the subject): Hispanic or Latino, not Hispanic or Latino.

11.2.2 Medical history

All relevant past and concurrent medical history must be recorded and includes:

- Any ongoing AEs from parent trial. In addition, AEs reported after completion of the parent trial and prior to signing the informed consent form in the present trial must be recorded as medical history.
- Skin disease history: all past and current skin disease history should be collected, including (but not limited to) alopecia, vitiligo, and herpes simplex infection.
- Atopy history:
  - Duration of AD in years.
  - Previous AD treatments.
  - Asthma.
  - Food allergy.
  - Hay fever.
  - Allergic conjunctivitis.
  - Atopic keratoconjunctivitis.
  - Eczema herpeticum.
- Other medical and surgical history, including concurrent diagnoses.

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

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

11.2.3 Height

The subject's height (without shoes) will be measured.

11.2.4 Columbia-Suicide Severity Rating Scale

The C-SSRS Screening version is a rater-administered instrument used to assess the lifetime history and severity of suicidal ideation and suicidal behaviour through a series of simple, plain-language questions (Posner et al. 2007). The C-SSRS must be completed at screening to

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

11.3 Efficacy assessments

11.3.1 Investigator assessments

11.3.1.1 Investigator's Global Assessment

The IGA is an instrument used in clinical trials to rate the severity of the subject's global AD and is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Panel 11). 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.

Panel 11: 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).

11.3.1.2 Eczema Area and Severity Index

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (Hanifin 2001). 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 12. 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 13. For each body region, a severity sum score will be calculated which will be multiplied by an area score (Panel 13) and by a weighting factor. The EASI score equals the sum of the scores obtained for each body region (Panel 12).

Panel 12: Calculation of the Eczema Area and Severity Index

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

Abbreviations: AS = area score; EASI = Eczema Area and Severity Index; SS = severity score.
Modified from the Harmonising Outcome Measures for Eczema.

Panel 13: 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, and 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.

11.3.1.3 Scoring Atopic Dermatitis

The SCORAD is a validated tool to evaluate the extent and severity of AD lesions, along with subjective symptoms (European Task Force on Atopic Dermatitis 1993). The maximum total score is 103, with higher values indicating more severe disease. SCORAD will be assessed according to the schedule of trial procedures (Section 4).

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

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

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

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

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

Note: dryness is evaluated on uninvolved areas.

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

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

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

11.3.2 Patient-reported outcomes

11.3.2.1 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 (Charman et al. 2004). 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 higher score indicates worse disease severity. The POEM will be completed at the trial site 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.

11.3.2.2 Dermatology Life Quality Index/Children's Dermatology Life Quality Index

Adult subjects from all parent trials, except the parent trial LP0162-1334, will perform the Dermatology Life Quality Index, DLQI. 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 quality of life over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment (Finlay and Khan 1994). 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 higher score indicates poorer quality of life. The DLQI will be completed at the trial site 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.

All subjects from the parent trial LP0162-1334, independent of the subject's age during participation in ECZTEND, will perform the Children's Dermatology Life Quality Index, CDLQI. The CDLQI questionnaire is designed and validated in subjects with dermatological conditions from 5 to 16 years (Lewis-Jones et al 1995, Salek et al 2013, Waters et al 2010). The CDLQI is available in text and cartoon versions (Holme et al 2003, Beattie and Lewis-Jones 2006, Clayton et al 2007). The text version will be used in this trial. It consists of 10 items addressing the subject's perception of the impact of their skin disease on various aspects of their QoL over the last week such as dermatology-related symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and the treatment (CDLQI Information and

Instructions 2018). Each item is scored on a 4-point Likert scale (0 = 'not at all'; 1 = 'only a little'; 2 = 'quite a lot'; 3 = 'very much'). The item on school time (item 7) has one additional response category 'prevented school', which is also scored '3'. The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor QoL. The CDLQI will be completed by subjects from the parent trial LP0162-1334 at the trial site according to the schedule of trial procedures in Section 4.

11.3.2.3 EuroQoL 5-Dimension Health Questionnaire 5-Level

The EQ-5D-5L is a standardised measure of health status developed by the EuroQol group to provide a simple, general measure of health for clinical and economic appraisal (Greiner et al. 2003). The EQ-5D-5L is a self-reported 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. Subjects from the parent trial LP0162-1334 will not perform the EQ-5D-5L, as this questionnaire has not been validated for adolescents.

11.3.2.4 Other patient-reported outcomes

Subjects will be asked about their recalled sleep interference, itch severity, and use of topical treatments during the last week prior to each site visit (from 6 days prior to each visit and including the day of the visit, referred to below as 'during the past week'), using the following PROs:

Eczema-related Weekly Sleep numeric rating scale
Subjects will rate how much their eczema interfered with their sleep during the past week using an 11-point numeric rating scale (NRS), using whole numbers only, with 0 indicating that it 'did not interfere' and 10 indicating that it 'completely interfered'. Subjects from the parent trial LP0162-1334 will perform an NRS with phrasings tailored to adolescent subjects, independent of the subject's age during participation in ECZTEND.

Worst Weekly Pruritus numeric rating scale
Subjects will assess their worst itch severity during the past week using an 11-point NRS, using whole numbers only, with 0 indicating 'no itch' and 10 indicating 'worst itch

imaginable'. Subjects from the parent trial LP0162-1334 will perform an NRS with phrasings tailored to adolescent subjects, independent of the subject's age during participation in ECZTEND.

Patient use of topical treatment
Subjects will state their use of TCS or TCI ('yes', 'no') during the past week.

These PROs will be presented to subjects and recorded on paper, and site staff will transcribe the data into the eCRF.

11.4 Safety assessments

11.4.1 Weight

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

11.4.2 Vital signs

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

For the first 3 tralokinumab dosing visits, subjects will be monitored for immediate drug reactions for a minimum of 30 minutes after administration of tralokinumab, with vital signs measured after 30 minutes or until stable, whichever is later (Section 9.2). Subjects who have participated in open-label tralokinumab arms of trials LP0162-1325, -1326, or -1334 or from one of the open-label trials LP0162-1342 and TRA-WEI-0015-I, and who have received at least 3 doses of tralokinumab in the parent trial, are exempt from this monitoring.

If an abnormal vital sign at screening is considered clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be included in the trial (in accordance with exclusion criterion no. 28).

In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later with subjects resting in a supine or sitting position to verify the first measurement. Should the repeated measurement result in a normal value, the measurement must be repeated approximately 15 minutes after the second measurement with subjects resting in a supine or sitting position. 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. If vital signs were not assessed, a reason should be given. Clinically significant abnormal vital signs at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom, or illness will be reported as an AE in accordance with Section 13.3.

11.4.3 Physical examination

A thorough physical examination of the subject including whole body inspection of the skin; auscultation of the heart, lungs, and abdomen; palpation of the abdominal organs; and assessment of 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 included in the trial (in accordance with exclusion criterion no. 28).

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

Clinically significant abnormal physical examination findings at the screening visit will be documented as medical history in the eCRF. If an abnormal physical examination finding at any other visit than the screening visit is considered clinically significant by the investigator, 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 will be reported as an AE in accordance with Section 13.3.

11.4.4 Electrocardiogram

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

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

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

The investigator must evaluate all abnormal ECG results ('clinically significant' or 'not clinically significant') and sign and date the evaluation. The investigator has the final decision on the clinical significance of ECG abnormalities. If a result is abnormal at the screening visit and considered clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be included in the trial (in accordance with exclusion criterion no. 28); if such a subject is included, the investigator will provide a justification in the medical record.

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

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

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

11.4.5 Laboratory testing

11.4.5.1 Overview

Blood and urine samples will be collected according to the schedule of trial procedures (Section 4). The evaluations shown in Panel 14 will be performed.

Panel 14: 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 Low density lipoprotein (LDL) cholesterol High density lipoprotein (HDL) cholesterol Triglycerides Glucose (non-fasting) Albumin Protein Tryptase[2]	Erythrocytes Haematocrit Haemoglobin Erythrocyte mean corpuscular volume Erythrocyte mean corpuscular haemoglobin concentration Leucocytes Neutrophils Neutrophils/leucocytes Lymphocytes Lymphocytes/leucocytes Monocytes Monocytes/leucocytes Eosinophils Eosinophils/leucocytes Basophils Basophils/leucocytes Thrombocytes
	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 Leucocytes Nitrite	Choriogonadotropin beta

[1] If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.

[2] Only measured in case of suspected anaphylaxis (Section 9.2).

[3] Urine samples will be tested at the trial site (dipstick). Until end of May 2021, in case of abnormal dipstick results, a urine sample will be sent to the central laboratory for microscopic examination (leucocytes, erythrocytes, and casts). After May 2021, a urine sample will only be sent to the central laboratory to perform urinalysis if considered required by the investigator based on the urine dipstick results.

[4] Measured at screening only. In case additional analysis are needed to support the interpretation of the initial test results for hepatitis B, hepatitis C, or HIV, these will be performed by the central laboratory as applicable.

[5] Not measured at screening.

[6] Only female subjects of childbearing potential.

Abbreviations: HIV = human immunodeficiency virus.

11.4.5.2 Urine pregnancy test

Female subjects of childbearing potential will have a urine pregnancy test (human chorionic gonadotropin; dipstick) performed at the trial site at baseline prior to treatment assignment. The test will be repeated at Week 4 and thereafter the schedule of pregnancy testing is as shown in the schedule of trial procedures (Section 4). After May 2021, subjects must in addition to the test performed at the trial site, perform the urine pregnancy test at home within 48 hours before the telephone visit using the kit supplied by the site staff. The subject will also be provided with a urine pregnancy test instruction. The result of the pregnancy test should be communicated to the site during the telephone visit and documented in the eCRF and source documents.

For female subjects who become of childbearing potential during the trial (defined as Tanner stage ≥3 [Marshall 1969] or menarche), the investigator must reassess whether contraceptive measures are in place (if applicable), and perform the pregnancy tests according to the schedule of trial procedures (Section 4).

Note that pregnant subjects must permanently discontinue IMP and be withdrawn from the trial immediately (see Section 10.2.2).

11.4.5.3 Investigator evaluation of laboratory samples

Central laboratory
Chemistry, haematology, urinalysis (if applicable), serology, and serum pregnancy tests will be analysed by a central laboratory, which will provide results to the trial sites. The investigator must evaluate all results outside the reference range (‘clinically significant’ or ‘not clinically significant’) and sign and date the evaluation. The signed and dated version will be filed with the investigator’s trial documentation. Clinically significant abnormal tests at baseline or later must be repeated to confirm the abnormality.

At each visit, the site staff will record in the eCRF if a sample was taken and, if applicable, the date and time as well as the investigator’s assessment of the results (‘normal’, ‘abnormal, not clinically significant’, ‘abnormal, clinically significant’).

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 included in the trial (in accordance with exclusion criterion no. 28).

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

Tests performed at the trial site
Urine samples will be tested at the trial site with a dipstick. Until end of May 2021, in case of abnormal dipstick results, a urine sample was sent to the central laboratory for microscopic examination (leucocytes, erythrocytes, and casts). After May 2021, a urine sample will only be sent to the central laboratory to perform urinalysis if considered required by the investigator based on the urine dipstick results.

At each site visit, the site staff will record in the eCRF if a urine sample was taken and, if sent for central laboratory analysis following an abnormal dipstick result, the investigator's assessment of the central analysis result ('normal', 'abnormal').

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

11.4.6 Anti-drug antibodies measurements

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

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

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

11.5 Pharmacokinetic assessments

Blood samples for PK assessments should 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 the sample was not taken, 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 validated bioanalytical methods. Details of the analytical methods used will be described in the bioanalytical report.

11.6 Skin biopsies (subgroup of subjects at selected sites)

At selected sites, the subgroup of subjects who donated skin biopsy samples in the parent trial LP0162-1325 will be asked to have skin biopsies taken in trial LP0162-1337 as well. The objective of collecting these additional biopsies is to investigate the molecular profile in the skin of AD patients treated for more than 1 year with tralokinumab and to document the long-term disease control of tralokinumab. Participation in this part of the trial requires that the subject provides additional informed consent.

Two 3 mm skin biopsies (1 from lesional skin and 1 from non-lesional skin) will be taken at Week 48 as specified in the schedule of trial procedures (Section 4). The locations of the biopsies taken should be in close proximity to the locations of the biopsies taken in trial LP0162-1325.

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

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

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

Gene expression analysis

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

The results from the analyses of biopsy material will be presented in a separate report.

11.7 Estimate of total blood volume collected

Blood samples will be drawn for analysis of safety (chemistry, haematology, and serology), PK, and ADA.

The total volume of blood to be drawn for each subject will depend on the time of their entry in the trial and the local duration of the trial (Appendix 3J). For adult subjects, the total blood volume drawn will be approximately 265 mL until end of May 2021, plus 70 mL per year of trial participation after May 2021. For adolescents, the total amount of blood drawn until end of May 2021 will be approximately 130 mL, plus 70 mL for the 1 year extension until end of May 2022.

The volume of blood drawn at any visit during the trial will be approximately 20 mL for all subjects. The maximum possible blood volume drawn at one visit is less than 1% of the total blood volume, and the maximum possible blood volume drawn within 4 weeks is less than 3% of the total blood volume, as recommended for the age group 0–18 years (European Commission 2008).

11.8 End of trial

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

- Date of last administration of IMP.

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

- Did the subject complete the trial?
  - *If not*: primary reason for withdrawal from trial (lack of efficacy, AE, withdrawal by subject, withdrawal by parent/guardian*, lost to follow-up, death, other).
- Did the subject attend the safety follow-up visit?
  - *If not*: primary reason for not attending safety follow-up visit (lack of efficacy, AE, withdrawal by subject, withdrawal by parent/guardian*, lost to follow-up, death, other).
- Date of last contact.

*For adolescent subjects as applicable.

The end of trial form will be completed when the subject has had their last visit (see Section 7.3).

11.9 Storage of biological samples

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

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

Skin biopsy 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 unless specific additional consent has been obtained that allows storage for future research (see below).

Biobank
If consent is given by the subject, LEO Pharma will store skin biopsy samples in the biobank established by LEO Pharma and hosted by BioStorage Technologies, Inc. Donation of the samples for future research is voluntary and subjects must give their separate written consent to confirm donation and storage and the terms associated herewith. The samples will be transferred from the relevant laboratory to the biobank. The samples will be labelled with the trial ID, subject ID, and the sample date to protect the privacy of the subjects and to allow continued blinding for future analyses.

12 Scientific rationale for trial design and appropriateness of assessments

This trial is open-label to ensure the generation of long-term safety data without treating subjects with placebo for a prolonged period of time. The trial includes adolescent and adult subjects who have already participated in a clinical trial (parent trial) with tralokinumab. The eligibility criteria are chosen to ensure that subjects from the parent trials can safely be included in this long-term trial. Subjects will have the possibility to use tralokinumab both with and without TCS (US class ≥4 or Europe class ≤3), reflecting the intended use of tralokinumab in real clinical practice.

Long-term safety will be assessed using standard clinical methods of subject evaluations, such as AE monitoring, ECG, vital signs, and clinical laboratory measurements. Furthermore, data on antibodies against tralokinumab (ADAs) will be collected and the potential for immunogenicity will be evaluated until the end of the safety follow-up period. The serum samples for determination of presence or absence of ADA, along with blood concentrations of tralokinumab, will be analysed using validated bioanalytical methods.

The clinical efficacy of tralokinumab treatment will be assessed using 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 (Hanifin et al. 2001). SCORAD is a validated tool to assess the extent and severity of AD lesions and subjective symptoms (European Task Force on Atopic Dermatitis 1993). The efficacy endpoints IGA score of 0 or 1 and EASI75 are recognised as important endpoints in clinical trials in AD by regulators in the US, EU, and Japan.

The clinical efficacy of tralokinumab treatment will also be assessed using PROs related to disease symptoms, quality of life, general health status, itch, and sleep quality. POEM is a validated questionnaire used to assess disease symptoms in atopic eczema patients in both clinical practice and clinical trials (Charman et al. 2004), and is recommended by the Harmonising Outcome Measures for Eczema for measuring patient-reported symptoms in eczema trials. DLQI/CDLQI is a validated and widely used questionnaire designed to measure the quality of life of dermatological patients (Finlay and Khan 1994, CDLQI Information and Instructions 2018). The EQ-5D-5L is a standardised measure of health status developed by the EuroQol group to provide a simple, general measure of health for clinical and economic appraisal (Greiner et al. 2003).

In order to be able to analyse the endpoints (change from parent trial baseline), subjects from the parent trial LP0162-1334 will continue to assess the CDLQI independent of the age of the subject during participation in ECZTEND. Subjects from the parent trial LP0162-1334 will

perform an adolescent's pruritis NRS with a recall period of the past 7 days, and an eczema-related sleep NRS with a recall period over the past 7 nights with phrasings tailored to adolescent subjects, independent of the subject's age during participation in ECZTEND. The EQ-5D-5L has not been validated for adolescents and was not assessed in trial LP0162-1334, and is therefore not to be performed in ECZTEND for subjects from the parent trial LP0162-1334.

The trial design has been modified with protocol version 10 to secure long-term safety data of up to 5 years globally. The treatment extension for subjects from the parent trials LP0162-1325, -1326, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I will be country-specific to allow for treatment with tralokinumab until tralokinumab is available to patients outside the clinical trial setting (Appendix 3J). Subjects from the ongoing adolescent parent trial LP0162-1334 are offered a total treatment extension of 1 year until end of May 2022.

The trial design was modified while the trial was ongoing (effective after May 2021) to decrease the burden of frequent site visits for subjects by introducing a visit schedule more similar to standard practice for home use. To ensure close safety monitoring throughout the treatment period, a mandatory telephone visit will be performed in between site visits.

13 Adverse events

13.1 Definition and classification of adverse events

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

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

13.2 Collection of adverse event reports

AEs must be collected from the time of first trial-related activity after the subject or subject's legal representative(s) has signed the informed consent form (ICF) until completion of the clinical trial, as defined in Section 7.3. To avoid duplicate reporting, however, any AE with onset before the final visit (safety follow-up visit) in the parent trial should be reported as an AE in the parent trial; for subjects without a safety follow-up visit in the parent trial, any AE with onset before the baseline visit in ECZTEND should be reported as an AE in the parent trial. If ongoing, the AE should also be recorded as medical history in the current extension trial (see Section 11.2.2). AEs with onset after the final visit in the parent trial and after informed consent has been obtained for the present trial, should be recorded as an AE in ECZTEND.

AEs must be assessed by medically qualified personnel.

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

Clinically significant abnormal findings related to vital signs, physical examination, ECGs, or laboratory tests after the screening visit must be reported as an AE, as described in Sections 11.4.2 to 11.4.5.

13.3 Reporting of adverse events

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

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

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

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

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

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

13.4 Reporting of serious adverse events

The criteria that define an AE as serious (that is, an SAE) are defined in Appendix 1. SAE criteria are also listed on the SAE Form. On the SAE form in the present extension trial, information regarding the subject's ID and parent trial ID must also be provided.

13.4.1 Investigator reporting responsibilities

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

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

Global Safety at LEO Pharma

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

Fax number: +45 6910 2468

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

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

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

SAEs occurring after the completion of the clinical trial, as defined in Section 7.3, should not be routinely sought or collected. However, such events should be reported to Global Safety at LEO Pharma (see contact details above) if the investigator becomes aware of them.

13.4.2 LEO Pharma reporting responsibilities

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

For the IMP, the Investigator's Brochure, edition 19 and subsequent updates must be used.

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

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

For all non-US countries, the following reporting requirements apply: all SAEs which are assessed as causally related to the IMP(s) **by either the investigator or LEO Pharma** (ICH E2A Guideline), and which are unexpected (Suspected, Unexpected Serious Adverse Reactions [SUSARs]), are subject to expedited reporting to regulatory authorities and IEC(s)/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 IMP(s) **by LEO Pharma** (Guidance for Industry and Investigators - Safety Reporting Requirements for INDs and BA/BE Studies; Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection) and which are unexpected (Serious and Unexpected Suspected Adverse Reactions [IND safety report]) are subject to expedited reporting to regulatory authorities and IRB(s). Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

13.5 Expedited reporting of pregnancy

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

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

Pregnant subjects must immediately discontinue IMP permanently (Sections 10.2.2 and 10.3).

13.6 Reporting of other events

13.6.1 Adverse events of special interest

The events listed in Panel 15 are considered adverse events of special interest (AESIs) in this trial and will require additional details to be recorded in the eCRF. LEO Pharma may request that the investigator forward test results, as appropriate. An AESI may be serious (requiring expedited reporting, Section 13.4) or non-serious.

Panel 15: Adverse events of special interest

Adverse event of special interest	Additional data to be recorded in eCRF (if available[1])
Eczema herpeticum	Skin findings: • Lesion type (papules, vesicles, crusts, eroded pits, other). • Disseminated/localised. • Location (face, scalp, back, chest, upper limb, lower limb, genitals). • Present in an area with visible eczema / no visible eczema / present in areas with and without eczema. • Monomorphic/polymorphic. Confirmation of herpes simplex virus (not confirmed, PCR, viral culture, Tzanck, other).
Malignancy diagnosed after treatment assignment, 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.

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

Abbreviations: eCRF = electronic case report form; PCR = polymerase chain reaction

13.6.2 Overdose

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

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

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

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

13.6.3 Medication error

Medication error refers to any unintentional error in the dispensing or administration of an IMP while in the control of the investigator or subject. Broadly, medication errors fall into 4 categories: wrong medication, wrong dose (including strength, form, concentration, amount, as well as administration with an interval of less than 7 days), wrong route of administration, or wrong subject.

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

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

13.6.4 Misuse

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

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

13.6.5 Abuse

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

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

13.6.6 Aggravation of condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s) (including the trial disease), compared with baseline, must be reported as an (S)AE in accordance with Sections 13.3 and 13.4.

AD is a fluctuating disease with possible periods of remission. In case of relapses/recurrences, only aggravations/exacerbations exceeding normal disease fluctuation or lesions appearing in a body area normally not affected by AD should be reported as an AE.

13.7 Follow-up for final outcome of adverse events

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

13.8 Handling of an urgent safety measure

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

appropriate urgent safety measures to protect the subjects against any immediate hazard" (European Parliament and Council of The European Union 2001).

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 Pharma, regulatory authorities, or IRBs/IECs.

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

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

14 Statistical methods

14.1 Sample size

The assumed size of this trial is approximately 1,600 subjects. No formal sample size has been calculated; the sample size is based on the population sizes of the parent trials and assumptions regarding how many subjects will complete the parent trials and be eligible for / consent to participate in the current trial.

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All subjects receiving tralokinumab will be included in the full analysis set (FAS) and will be analysed for efficacy. Exclusions from the FAS can be considered in special cases as described in ICH E9, section 5.2.1., Full Analysis Set. If it is decided to exclude a subject who has received tralokinumab from the FAS, a justification addressing ICH E9 will be given.

The safety analysis set will be identical to the FAS and will be used for summarising safety.

Data from the investigator-initiated parent trial TRA-WEI-0015-I will not be transferred to LEO Pharma. Thus, endpoints defined as change from baseline (in parent trial) will not be calculated for subjects from this trial, and data from this trial will not be included in tables summarising endpoints defined as change from baseline or where data are presented by responder/non-responder. Subjects from this parent trial will be contributing to the primary endpoint and included in summary tables where possible.

The decisions regarding inclusion/exclusion of subjects or subject data from the trial analysis sets will be documented in an analysis set definition document.

14.3 Statistical analysis

14.3.1 Disposition of subjects

The reasons for withdrawal from the trial will be presented for all subjects assigned treatment.

14.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics (age, sex, ethnicity, race) and the latest treatment regimen in the parent trial (placebo, tralokinumab, tralokinumab + TCS) will be presented for the total cohort of subjects and by tralokinumab-naïve/re-treated/continuously treated subjects. For the re-treated and continuously treated subjects, the presentation will further be

divided by responder/non-responder in the parent trial; clinical response is defined as achievement of IGA 0/1 or EASI75 at the last assessment in the parent trial.

14.3.3 Exposure and treatment compliance

Exposure
Exposure to treatment will be presented for the safety analysis set as days of exposure in total, by yearly treatment period, and by parent trial.

Days of exposure will be calculated as the number of days from the date of the first IMP dose to the date of the end of treatment visit, or – if the end of treatment visit is missing – to the date of permanent discontinuation of IMP.

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

Adherence will be presented for the safety analysis set.

14.3.4 Primary endpoint

The primary endpoint in this trial is number of adverse events during the treatment period from baseline up to Week 268, and the analysis of this is covered in Section 14.3.8.

14.3.5 Secondary efficacy endpoints

The analyses of the secondary efficacy endpoints will be done for the FAS as well as for the observed cases. Subjects fulfilling the stopping rules (see Section 10.2.1) will be withdrawn from trial, and no observed data will be available after withdrawal. As a consequence, subjects withdrawn will be regarded as non-responders in the FAS analysis.

IGA and EASI75 will be presented as response rates with 95% confidence intervals at each assessment visit. The results will be presented for the total cohort of subjects and by tralokinumab-naïve/re-treated/continuously treated subjects. For the re-treated and continuously treated subjects the results will further be divided by responder/non-responder in the parent trial; clinical response is defined as achievement of IGA 0/1 or EASI75 at the last assessment in the parent trial.

In the evaluation of EASI75, the baseline score will be that from the parent trial.

14.3.6 Other endpoints

Changes from baseline in EASI score and SCORAD will be presented as number of observations (N), mean, standard deviation (SD), median, minimum, and maximum at each assessment visit. The baseline scores used will be those from the parent trial.

The changes from baseline in EASI score and SCORAD will be presented for the FAS as well as for the observed cases.

3 endpoints addressing treatment effect during the treatment period will be included:

- Proportion of time with EASI75 after first occurrence of EASI75 during treatment.
- Proportion of time with EASI50 after first occurrence of EASI50 during treatment.
- Proportion of time with IGA 0/1 after first occurrence of IGA 0/1 during treatment.

The proportion of time with EASI75 for an individual subject will be calculated as the time with EASI75 (that is, the sum of time intervals with EASI75) divided by the observation period after first occurrence of EASI75. The time intervals in which EASI75 is observed at the start of the interval will be accumulated and normalised with the total treatment time from first EASI assessment with EASI75 until end of treatment.

The proportion of time with EASI50 and with IGA = 0/1 after first occurrence during treatment will be determined using the same principle as for the proportion of time with EASI75.

These ‘proportion of time’ endpoints will each be presented as number of observations (N), mean, SD, median, minimum, and maximum. The group mean comprising the summed nominators (of time) divided by the summed denominators will further be presented.

As the frequency of site visits is reduced after May 2021, a sensitivity analysis excluding data captured after May 2021 will be performed for the ‘proportion of time’ endpoints. For exploratory purposes, the proportion of subjects achieving EASI75 will be plotted versus the proportion of time with EASI75 (ranging from 0–100% of the observation period after first occurrence of EASI75). Similar plots for EASI50 and IGA 0/1 will be shown in the same graph.

The results for the endpoints described in this section will be presented for the total cohort of subjects and by tralokinumab-naïve/re-treated/continuously treated subjects. For the re-treated

and continuously treated subjects, the results will further be divided by responder/non-responder in the parent trial (clinical response as defined in Section 14.3.5).

The primary reasons for discontinuation of IMP over time will be presented relative to the number of subjects receiving treatment at Week 0.

14.3.7 Patient-reported outcomes

Changes from baseline in POEM score, DLQI/CDLQI score, and EQ-5D-5L score will be presented in the same way as changes from baseline in EASI score and SCORAD (see Section 14.3.6). The baseline scores used will be those from the parent trial. In the special case where a subject has an assessment at both Week 80 and Week 88, the Week 80 assessment (corresponding to approximately 1½ years) will be used for the Week 80-88 endpoint evaluation. Likewise, the Week 128 assessment (~ 2½ years) will be prioritised for the Week 128-136 endpoint evaluation. The DLQI score will be presented for subjects from the parent trials LP0162-1325, -1326, -1339, -1341, -1343, and -1346. The CDLQI score will be presented for subjects from the parent trial LP0162-1334. As subjects from the parent trial LP0162-1342 did not have POEM, DLQI, or EQ-5D-5L assessments in the parent trial, the change from baseline is not applicable. As subjects from the parent trials LP0162-1334 and -1343 did not have EQ-5D-5L assessments in the parent trial, the change from baseline is not applicable. Changes from baseline will not be presented for subjects from the parent trial TRA-WEI-0015-I, since data from this investigator-initiated trial will not be transferred to LEO Pharma (see Section 14.2).

The Worst Weekly Pruritus NRS/adolescent's pruritis NRS score, the Eczema-related Weekly Sleep NRS/adolescent's eczema-related NRS score, and the change from baseline (in the current trial) in both scores will be summarised descriptively by visit as mean, SD, median, minimum, and maximum values.

The use of topical treatment during the last week as a binary score will be summarised descriptively by visit.

14.3.8 Safety

The analysis of safety will be based on the safety analysis set.

14.3.8.1 Adverse events

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

system organ class (SOC) as percentage of subjects with AEs, number of AEs, and rate of AEs (number of AEs per 100 patient-years of exposure).

Only treatment-emergent AEs will be summarised; however, all AEs recorded during the course of the trial will be included in subject data listings. An AE will be considered treatment-emergent if started after the first use of IMP, or if started before the first use of IMP and worsened in severity after first dose of IMP. The tabulations described in the following will only include treatment-emergent AEs. In each of the tabulations, AEs are defined by MedDRA preferred term within primary SOC.

An overall summary of the number of AEs, the rate of AEs (number of AEs per 100 patient-years of exposure), the number (percentage) of subjects with any treatment-emergent AEs, deaths, SAEs, withdrawals from the trial due to AEs, treatment-related AEs, and severe AEs will be presented. The above summaries will also be made separately for subjects who transferred from the parent trial LP0162-1334. As the frequency of site visits is reduced after May 2021, an additional overall AE summary table will be presented that excludes events and exposure time after May 2021. In addition to the overall summary, the data will be presented by tralokinumab-naïve/re-treated/continuously treated subjects.

The number of AEs, rate of AEs, and number of subjects with each type of AE will be tabulated for the total cohort of subjects and by tralokinumab-naïve/re-treated/continuously treated subjects.

The severity and causal relationship to IMP for each type of AE will be tabulated.

Related AEs are defined as AEs for which the investigator has not described the causal relationship to IMP as ‘not related’. The number of subjects with each type of related AE will be tabulated.

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

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 (in the current trial) to each visit will be summarised by visit as mean, SD, median, minimum, and maximum values. The changes will be presented for the total cohort of subjects and by tralokinumab-naïve/re-treated/continuously treated subjects.

14.3.8.3 Clinical laboratory evaluation

The change in each of the laboratory parameters from baseline (in the current trial) to each visit will be summarised as mean, SD, median, minimum, and maximum values. The changes will be presented for the total cohort of subjects and by tralokinumab-naïve/re-treated/continuously treated subjects.

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. The changes will be presented for the total cohort of subjects and by tralokinumab-naïve/re-treated/continuously treated subjects. Subjects with laboratory parameters outside the reference range will be listed.

14.3.8.4 Anti-drug antibodies

The presence of ADAs is an endpoint included to assess the immunogenicity of tralokinumab.

The ADA status will be summarised by treatment in parent trial and visits with ADA measurements according to the following categories:

ADA status	Description
Positive, pre-existing	ADA positive at baseline. No post-baseline ADA response ≥4-fold over baseline titre level. At least 1 non-missing post-baseline ADA assessment.
Positive, treatment-boosted	ADA positive at baseline. At least 1 post-baseline ADA response ≥4-fold over baseline titre level.
Positive, treatment emergent	ADA negative or missing at baseline. At least 1 positive post-baseline ADA response.
Negative	ADA negative or missing at baseline. All post-baseline ADA assessments negative.

For the entire trial, the ADA status will be summarised by treatment in parent trial according to the categories of ADA status as listed above and with the following subcategories of treatment-emergent status:

Treatment-emergent subcategory status	Description
Treatment-emergent, persistent	Positive ADA for at least 2 consecutive visits with ADA measurements, at least 10 weeks apart.
Treatment-emergent, indeterminate	Only the last ADA response positive.
Treatment-emergent, transient	Neither persistent nor indeterminate.

The association of ADA status across the trial (positive versus negative) with AEs/SAEs may be evaluated. The ADA-positive subjects across the trial may in this evaluation be divided into the categories given above. The associations between ADA and AE/SAEs may be summarised for persistently, indeterminately, and transiently positive subjects.

Serum samples that test positive for ADA will be analysed for neutralising antibodies (nAB). The test sample will be deemed positive or negative for the presence of nAB to tralokinumab relative to a pre-determined (in assay validation) statistically derived cut point.

For subjects in the safety analysis set with positive ADA status, the ADA titre, nAB status, tralokinumab concentration, IGA assessment, and EASI assessment will listed by subject and visit. The listing will include information about which parent trial the subjects transferred from and what treatment they received in the parent trial.

14.3.9 Pharmacokinetics

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

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

The PK data may 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.

14.3.10 Interim analysis

Interim evaluation and reporting of trial data will be perfomed (e.g. to support submissions for marketing approval or sharing of results at conferences). This will be documented.

14.3.11 General principles

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

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

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, or the CTR, depending on the type of change.

14.3.12 Handling of missing values

Missing values will not be imputed, but will be handled as described in Sections 14.3.5 and 14.3.6 by doing analyses on the FAS as well as on the observed cases.

15 References

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Appendix 1: Definitions of adverse events and serious adverse events

Adverse event definition

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

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavourable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures unless these were planned before the subject consented to trial participation.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 11.4.5.3).

Serious adverse event definition

An SAE is any untoward medical occurrence that

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation. Planned hospitalisation or planned prolonged hospitalisation do not fulfil the criteria for being an SAE but should be documented in the subject's medical record.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

- or
    - Is a medically important condition. Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias and convulsions that do not result in hospitalisation, development of drug dependency or drug abuse.
- Adverse events of special interest are described in Section 13.6.1.

Appendix 2: Classification of adverse events

Severity

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

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

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

Causality

The *causal relation* of the AE to the use of the IMP should be classified using the below categories of probable, possible, or not related according to the investigator's clinical judgement.

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, for example subject lost to follow-up.

Note that as per the above definition, LEO Pharma uses “RECOVERED/RESOLVED” only if an event has actually stopped. According to the CDISC definition, the category “RECOVERED/RESOLVED” also includes events which have improved. However, following the LEO Pharma definitions above, such an improved event will instead be classified as “NOT RECOVERED/NOT RESOLVED” or “RECOVERING/RESOLVING”.

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

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

Appendix 3: Trial governance considerations

Appendix 3A: Regulatory and ethical considerations

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

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

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

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

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

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

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

Appendix 3B: Informed consent process

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

The subject's signed and dated informed consent to participate in the clinical trial (or their legally authorised representative's signed and dated informed consent, if applicable) 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. The subject's decision not to participate or to withdraw will be respected, even if consent is given by the subject's legally authorised representative(s).

Subjects and their legally authorised representative(s) (if applicable) will be re-consented to the most current version of the ICF(s) (including the additional ICF for the subgroup of subjects having biopsy samples taken) during their participation in the trial, if applicable. A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative (if applicable).

Adolescent subjects must give their written assent as appropriate and according to national laws and regulation. The subject's signed and dated informed assent to participate in the clinical trial must be obtained prior to any clinical trial-related procedure being carried out in accordance with ICH GCP (Section 4.8) and all applicable laws and regulations. The adolescent subject will be re-consented to the most current version of the ICF(s) during the trial, if applicable and in accordance with national laws or regulations. A copy of the ICF(s) must be provided to the adolescent subject in accordance with national laws or regulations.

Subjects who become of legal age during the trial, will be consented to the most current version of the ICF for adult subjects, if required by national laws or regulations. Subsequently, these subjects will be re-consented to the most current version of the ICF(s) for adult subjects during the trial, if applicable.

To participate in the ECZTEND trial after May 2021, subjects must re-consent/consent to protocol version 10 to 13.

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.

Appendix 3C: Subject and data confidentiality

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

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

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

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

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

Processing of personal data
This protocol specifies the personal data on trial subjects (for example race, ethnicity, age, gender, health condition, medical history, test results, 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 Pharma and third parties acting on behalf of LEO Pharma.

Processing of personal data on behalf of LEO Pharma requires a written agreement between LEO Pharma and the relevant party which covers collection, processing, and transfer of personal data in the clinical trial as well as reporting obligations in the event of any data breach. In certain cases, an agreement on transfer of personal data may also be required.

Investigators and LEO Pharma must ensure that collection, processing, and transfer of personal data are in compliance with applicable legislation on data protection and privacy, including but not limited to the EU General Data Privacy Regulation.

Subjects (or their legally acceptable representative) 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 long-term clinical trial in AD involving open-label treatment with tralokinumab.
    - 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, for example 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 (for example by telephone).

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

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

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

Risk assessment
In this trial, overall risks have been assessed to ensure subject safety and will be continuously monitored during the trial.

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, the CRAs will verify that investigators work according to the protocol.

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

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

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

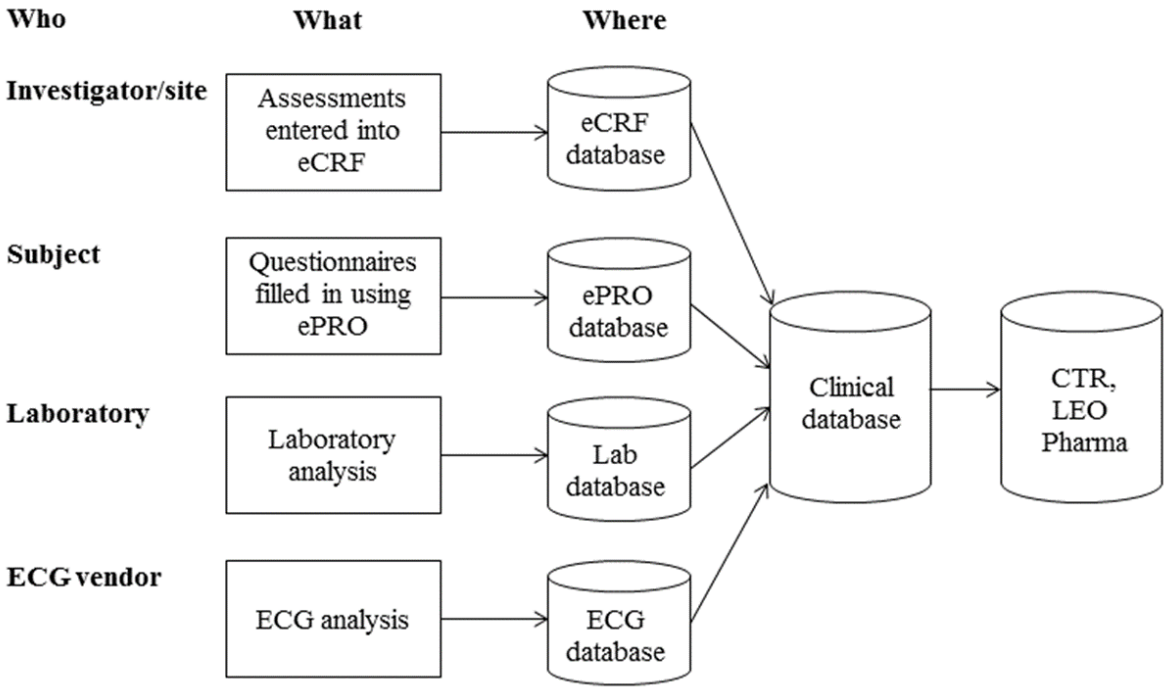
An electronic PRO (ePRO) solution will be used to capture patient-reported data from questionnaires completed at the trial site. By the use of ePRO, data will be available immediately after data entry and available for monitors and site personnel, including the investigator, with reader access only. 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.

Recalled PROs (Worst Weekly Pruritus NRS, Eczema-related Weekly Sleep NRS, and Patient use of topical treatment) will be recorded at each site visit and entered in the eCRF. The outcomes will be recorded for the period of 7 days before each site visit (from 6 days prior to each visit and including the day of the visit).

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

Transmissions of electronic data from external data providers and of ePRO data to the clinical database are illustrated in Panel 16.

Panel 16: Transmission of electronic data



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

Archiving of trial documentation

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

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

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

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

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 assigned subjects included 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 Pharma, from regulatory authorities and/or IRBs/ IECs.

Appendix 3E: Registration, reporting and publication policy

Trial disclosure

LEO Pharma 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 LEO Pharma corporate website in accordance with LEO Pharma's position on public access to clinical trial information no later than 6 months after trial completion. Trial results may also become reported in www.ClinicalTrials.gov, www.clinicaltrialsregister.eu and national data registries in accordance with applicable law and regulations after clinical trial completion or premature termination.

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

Publications

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

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

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

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

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

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

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

LEO Pharma complies with GPP3 standards and the recommendations from the International Committee of Medical Journal Editors. LEO Pharma complies with the positions of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), and the joint position statement by the American Medical Writers Association (AMWA), the European Medical Writers Association (EMWA), and the International Society for Medical Publication Professionals (ISMPP) on disclosure of information about clinical trials, trial results and authorship. LEO Pharma also follows the CONSORT reporting guidelines (Schulz 2010).

Appendix 3F: Insurance

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

Appendix 3G: Financial disclosure

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

Appendix 3H: Trial and site closure

Premature termination of trial or trial site

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

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

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

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

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

Completion of trial

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

Trial sites will be closed upon trial completion. LEO Pharma will undertake arrangements for the collection and disposal of any unused trial material that the investigator is not required to

keep in his/her files. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

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 3J: Country-specific end of treatment date

Subjects from the parent trial LP0162-1334, who consented to participate in the trial after May 2021, will end treatment by end of May 2022 in all countries.

Subjects from the parent trials LP0162-1325, -1326, -1339, -1341, -1342,-1343, -1346, and TRA-WEI-0015-I, who consented to participate in the trial after May 2021, will have a country-specific end of treatment date (Panel 17).

Panel 17: Country-specific last subject last treatment for parent trials LP0162-1325, -1326, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I

Country	Approximate last treatment date in the trial*
US	May 2022
Germany	Aug 2021
UK	Sep 2022
France	Aug 2022
Italy	Jan 2023
Belgium	Nov 2022
Canada	May 2023
Spain	Jan 2023
Poland	May 2024
Czech Republic	Oct 2022
Japan	May 2023

*These dates are estimates of availability of tralokinumab in the countries and could change.

Appendix 3K: COVID-19

Rationale

The current COVID-19 pandemic warrants many subjects in the ECZTEND trial to stay at home to comply with authority-issued preventive measures. This impacts subjects' ability to attend site visits in person. To follow authorities' restrictions and to safeguard the subjects in the ECZTEND trial as well as providing continued therapy to secure the scientific integrity, this clinical trial protocol appendix is installed to provide an opportunity for telephone visits and courier delivery of IMP and pregnancy tests to subjects in replacement of the site visits. In addition, inclusion criterion 2 is changed during COVID-19 restrictions, to allow subjects who are not able to attend all protocol-mandated visits of their parent trials due to COVID-19 to participate in trial LP0162-1337, if considered eligible for continued treatment by the investigator.

Subject eligibility

Inclusion criterion 2 in trial LP0162-1337 states:

- Subjects must have completed* the treatment period(s) of one of the parent trials: LP0162-1325, -1326, -1334, -1339, -1341, -1342, -1343, -1346, or TRA-WEI-0015-I.
    - * To be assessed on the first day of IMP administration (baseline).
- In trial LP0162-1334, a subject is considered to have completed the treatment period, if the subject has attended the Week 52 visit on site.
- In trials LP0162-1343 and TRA-WEI-0015-I, a subject is considered to have completed the treatment period, if the subject has attended the Week 16 visit on site.
- Change to inclusion criterion 2 in trial LP0162-1337 during COVID-19 restrictions:

The change to inclusion criterion 2 described in the following only applies to subjects coming from parent trials LP0162-1334, -1343, and TRA-WEI-0015-I, as these are the only parent trials ongoing at the time of this appendix.

For subjects who are not able to attend the above-mentioned visits at site in their parent trials due to COVID-19, inclusion criterion 2 is considered fulfilled if AEs have been collected over the telephone and if the investigator has evaluated and documented that the subject is considered to benefit from continued treatment in trial LP0162-1337, despite the missed visit(s) in the parent trial.

eCRF recording

It must be recorded in the eCRF if a site visit was converted to a telephone visit (not applicable for the scheduled mandatory telephone visits in protocol version 13). This should be done in the comments log for each visit. 'Visit date' must also be documented.

If the subject is reached by telephone, use of emollients, AEs, concomitant medication and pregnancy test result (if applicable) must be collected. All other assessments should be marked 'Not done' in the eCRF, except for EASI, SCORAD, IGA, and weight, which should be left blank. The log line 'If not done, specify reason' in the assessment form must be answered with 'COVID-19' as well as the specific reason related to COVID-19, e.g. subject cannot visit site due to COVID-19 quarantine, or site is closed due to COVID-19.

In addition, the specific COVID-19-related reason for missing visit or performing visit as telephone visit must be entered in the 'Comments log' in the eCRF on subject level.

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

Description of visit scenarios

It is a requirement that all subjects attend the first 3 dosing visits (Visit 3, 4, 5) at the clinic according to protocol in order to ensure the 30 min. post-dose observation time for the 3 dosing visits. This will at the same time ensure proper training prior to home use. If attending the first 3 dosing visits is not possible, then the subject cannot take part in the trial.

Without compromising the safety of subjects and site personnel, it is expected that efforts are made to secure visit attendance at sites for visits Weeks 16, 56, 88, 104, 136, 152, 184, 216 and 248, in order to secure important efficacy assessments for the trial. Depending on national guidelines regarding COVID-19 and subject preferences, the remaining visits can follow 2 different scenarios as described below:

1) The subject is <u>not restricted from attending visits at the clinic</u> and continues to follow all procedures specified in the protocol.

2) Subject is <u>not able to attend visits at the clinic,</u> in which case the following procedure must be followed:

    a. Site staff informs subject about the possibility of courier delivery of IMP and pregnancy test, if applicable.

b. The subject verbally consents to providing contact details for shipping purposes and to receiving IMP at home (this needs to be documented in the subject's medical records).

c. Site staff allocates IMP for the subject using the EDC system (RAVE®) as per protocol.

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

   i. Participant Information Sheet for home delivery.

   ii. Log of Drug Administration.

   iii. The appropriate amount of IMP.

   iv. One sharps container, if required.

   v. If required, sanitisers: alcohol wipes, cotton balls or gauze.

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

e. Site staff contacts the subject (by telephone) and ensures the following:

   i. The Participant Information Sheet has been read, is understood and agreed to.

   ii. Subject is asked about concomitant medication use, concomitant procedures, adverse events, and pregnancy test outcome according to the original schedule of trial procedures.

f. Site staff documents all the above in the subject's medical record at the clinic.

g. Site staff enters all available information into the EDC system (RAVE®), see above Section "eCRF recording".

Home use of IMP

Injections of tralokinumab

Self-injection of tralokinumab is described in the protocol and does not change with this appendix.

Subjects who miss one or more doses need to have the missed doses documented in the eCRF with specific reason related to COVID-19 written in the comments log for each visit in scope.

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

TCS

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

Emollients

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

Urine pregnancy test

The schedule of pregnancy testing does not change with this document. Subjects need to perform the urine pregnancy test kit at home if required per protocol. Urine pregnancy test kit is delivered by the site as per protocol. The subject will be provided with a Urine Pregnancy Test Instruction. Results should be communicated to the site by subject during telephone visit and documented in the eCRF and source documents.

Appendix 4: Country-specific requirements

This appendix describes requirements and procedures that are specific for Japan (Appendix 4A) and France (Appendix 4B). For each section, the text from the protocol is presented in normal font. The specific requirements or procedures for Japan or France are presented below in bold font.

Appendix 4A: Japan

Section 9.8.3 Drug accountability

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

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

Section 9.8.5 Trial product destruction

Used syringes will be destroyed at the trial site provided the trial site has procedures in place for such IMP destruction. Trial sites that do not have such IMP destruction procedures in place will dispose used IMP in sharps bins that will be shipped to the CMO.

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

Section 9.10 Reporting product complaints

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

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

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

Fax number: +81 3 4243 3311
E-mail address: clinical_trial_jp@leo-pharma.com

Section 11.1 Overview

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

- PROs in the following order:
    7. Patient Oriented Eczema Measure (POEM).
    8. Dermatology Life Quality Index (DLQI)/Children's Dermatology Life Quality Index (CDLQI).*
    9. EuroQoL 5-Dimension Health Questionnaire 5 Level (EQ-5D-5L)*.
    10. Eczema-related Weekly Sleep numeric rating scale (NRS).*
    11. Worst Weekly Pruritus NRS.*
    12. Patient use of topical treatment.
- *All subjects from the parent trial LP0162-1334, independent of the subject's age during participation in ECZTEND, will perform the Children's Dermatology Life Quality Index (CDLQI), an adolescent's pruritis NRS with a recall period of past 7 days, and an eczema-related sleep NRS with a recall period over the past 7 nights; these subjects will not perform the EQ-5D-5L as this questionnaire has not been validated for adolescents.
- Investigator assessments (performed only by adequately trained investigators; to reduce inter-rater variability, the same investigator should preferably perform all the evaluations for a given subject throughout the entire trial period) in the following order:
    1. SCORAD component C, then component A and B.
    2. IGA.
    3. EASI.
- Safety and laboratory assessments.
- Administration and dispensing of IMP.

In Japan, the order of assessments may be changed after the baseline visit to perform safety and laboratory assessments before the investigator assessments but after the PROs. The assessments must be performed in the same order for all subjects at the site.

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 or training in use of the assessments required by the protocol and must be either a physician, certified physician's assistant, or advanced registered nurse practitioner.

In Japan, investigators must be dermatologists.

Section 13.4.1 Investigator reporting responsibilities

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

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

Fax number: +81 3 4243 3311
E-mail address: clinical_trial_jp@leo-pharma.com

Section 13.4.2 LEO Pharma reporting responsibilities

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

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

Section 13.5 Expedited reporting of pregnancy

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

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

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

Fax number: +81 3 4243 3311
E-mail address: clinical_trial_jp@leo-pharma.com

Appendix 4B: France

Section 11.4.5.2 Urine pregnancy test

The test will be repeated at Week 4 and thereafter as shown in the schedule of trial procedures (Section 4).

In France, urine pregnancy testing will be repeated every 4 weeks. Thus, from Week 16 onwards, site staff will supply a pregnancy test kit for home use to female subjects of childbearing potential. The subjects will take the pregnancy test at home every 4 weeks following Week 16, and will record the results in the log of drug administration (in which they will record each IMP administration at home, as described in Section 9.8.4).

In case of a positive test result, the subject must discontinue IMP use and contact site staff immediately. Should this occur, site staff will call the subject in for an unscheduled site visit. In case of a negative test result, the subject should continue administration of IMP at home as usual.

Appendix 5: Eligibility criteria

A short form (200 characters) version of each of the eligibility criteria for the trial, using CDISC controlled terminology, is provided below.

No.	Inclusion criteria
1	Signed and dated informed consent has been obtained prior to any protocol-related procedures
2	Subjects must have completed the treatment period(s) of one of the parent trials: LP0162-1325, -1326, -1334, -1339, -1341, -1342, -1343, -1346 or TRA-WEI-0015-I (to be assessed at baseline)
3	Subjects must have complied with the clinical trial protocol in the parent trial to the satisfaction of the investigator
4	Be able and willing to self-administer tralokinumab treatment (or have it administered by a caregiver) at home after the initial 3 injection visits at the trial site (in this trial)
5	Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days prior to baseline
6	Female subjects of childbearing potential must use highly effective birth control for at least 1 month before baseline, throughout the trial, and for at least 16 weeks after last administration of IMP

No.	Exclusion criteria
1	Any condition that required permanent discontinuation of trial treatment in the parent trial
2	More than 26 weeks have elapsed since the subject received the last IMP injection in the parent trial (to be assessed at baseline)
3	Development in the parent trial of SAE that was deemed related to IMP and, as judged by investigator, could indicate an unreasonable risk of continued treatment
4	Development in the parent trial of AE that was deemed related to IMP and led to temporary discontinuation of IMP and, as judged by investigator, could indicate unreasonable risk of continued treatment
5	Receipt of any marketed or investigational biologic agent (such as cell-depleting agents or dupilumab) within 6 months prior to baseline, or until cell counts return to normal, whichever is longer
6	Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroids within 5 half-lives prior to baseline
7	Treatment with topical PDE-4 inhibitors or topical JAK inhibitors within 2 weeks prior to baseline

No.	Exclusion criteria (continued)
8	Positive HBsAg, HBsAb*, HBcAb, or anti-HCV serology at screening. Subjects with positive HBsAb are eligible provided they are vaccinated against hepatitis B and have negative HBsAg and HBcAb *Subjects from the parent trial LP0162-1343 with a positive HBsAb may be assigned treatment provided they have negative HBsAg, HBcAb, and HCV serology at screening.
9	Known or suspected hypersensitivity to any component of the IMP
10	History of anaphylaxis following any biological therapy
11	History of immune complex disease
12	History of cancer
13	Tuberculosis requiring treatment within 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care
14	History of any known primary immunodeficiency disorder including a positive HIV test at screening, or use of antiretroviral medications
15	Current participation in any other interventional clinical trial, except for tralokinumab trials LP0162-1325, -1326, -1334, -1339, -1341, -1342, -1343, -1346, or TRA-WEI-0015-I
16	Previously screened in this clinical trial
17	Receipt of live attenuated vaccines within 30 days prior to baseline and during the trial, including the safety follow-up period
18	Receipt of blood products within 4 weeks prior to screening
19	Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period
20	History of subject or subject's legal representative(s) of chronic alcohol or drug abuse within 12 months prior to screening, or any condition (e.g., psychotic state, language barrier or other) associated with poor compliance, as judged by the investigator
21	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
22	Subjects who are legally institutionalised
23	Female subjects who are pregnant, breastfeeding, or lactating
24	History of attempted suicide or significant risk of suicide (either in the opinion of the investigator or according to the C-SSRS)
25	History of a clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to baseline

No.	Exclusion criteria (continued)
26	A helminth parasitic infection within 6 months prior to the date when informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy
27	Any disorder that is not stable and in the investigator's opinion could affect the safety of the subject, influence the findings of the trial, or impede the subject's ability to complete the trial
28	Any abnormal finding which in the investigator's opinion may put the subject at risk, influence the results of the trial, or influence the subject's ability to complete the trial

Appendix 6: Guidance for anaphylaxis diagnosis

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

Clinical criteria for diagnosing anaphylaxis

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

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

AND AT LEAST ONE OF THE FOLLOWING:

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

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

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

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

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

Appendix 7: Contact list

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

Sponsor

LEO Pharma A/S (referred to as 'LEO Pharma' or 'the sponsor' in this clinical trial protocol) is the sponsor of the clinical trial:

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

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

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

Coordinating investigator

PPD

Appendix 8: Protocol amendment history

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

Amendment 1 (27-Jun-2018)

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

Overall rationale for the amendment:

The main reason for this amendment is to change an inclusion criterion that will enable all eligible subjects to enter this trial directly after completing the treatment period(s) in their parent trial. The scientific rationale for this change is given in the table below.

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

Note: The table below describes the changes in each section, either summarised (in plain text) or marked as tracked changes (text deleted has ~~a line through it~~).

Section no. and name	Description of change	Brief rationale
1 Protocol synopsis 5.3 Trial rationale 5.4 Justification for dose 8.2 Inclusion criteria Appendix 5	Change to inclusion criterion no. 2: Subjects from ALL parent trials will be eligible if they have completed the treatment period(s) in the parent trial. It is no longer a requirement that subjects from trials LP0162-1325, -1326, and -1339 must also have completed the safety follow-up period in the parent trial.	The original protocol required subjects from 3 of the parent trials to complete a 14-week, off-treatment period before they could enter the extension trial. This period was needed for tralokinumab concentrations to decrease to a level where the presence or absence of ADA could be determined in serum samples. A new ADA assay with improved tralokinumab tolerance has been developed. This means that ADA can be measured in serum samples with higher levels of tralokinumab. Therefore, the samples can be taken only 2 weeks after the last dose of tralokinumab, that is, at the end of treatment visit in the parent trials. Hence, subjects can transfer directly into the extension trial after completing the treatment periods in these 3 parent trials.
1 Protocol synopsis 4 Schedule of trial procedures 6 Trial objectives and endpoints 7.3 End of trial definition 14.3.4 Primary endpoint	Change in timeframe for primary endpoint from *up to Week 128* to *from baseline through the last treatment visit (up to Week 142)*.	To ensure that all treatment-emergent adverse events are included in the primary endpoint as well as to enable easier data presentation and reporting, it has been decided to include the entire treatment period for all subjects within the timeframe for the primary endpoint.

Section no. and name	Description of change	Brief rationale
4 Schedule of trial procedures	Change to urinalysis schedule: urinalysis assessment at Week 48 moved to Week 32.	Error in original protocol.
9.8.3 Drug accountability	Addition of text to specify that site staff will record the following details in the eCRF: the site of IMP injection, as recorded by subjects in the log of drug administration for each IMP administration at home.	Clarification that site staff will record these data in the eCRF.
14.3.3 Exposure and treatment compliance	Days of exposure will be calculated as the number of days from the date of the first IMP dose to the date of the end of treatment visit, or – if the end of treatment visit is missing – ~~to the date of the last IMP dose + 20 days* OR~~ to the date of permanent discontinuation of IMP, ~~whichever comes first~~. ~~* 20 days = planned time between 2 doses (14 days) + dosing window (±3 days) for both doses.~~	The definition of *exposure end* has been simplified, in line with updated statistical analysis plans for the parent trials.
14.3.8.1 Adverse events	Adverse events of special interest (AESIs) will be tabulated and listed instead of being presented in a narrative.	Tabulation and listings are considered a more practical and informative way of presenting data on AESIs. This will enable easier overview of the individual cases as well as sorting and pooling of data from several trials.
Throughout	Minor editorial revisions.	Minor, have therefore not been summarised.

Amendment 2 (31-Aug-2018)

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

Overall rationale for the amendment:

The main reason for this amendment is to change an inclusion criterion to also allow eligible subjects from trial LP0162-1346 to enter the extension trial. The scientific rationale for this change is given in the table below.

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

Note: The table below describes the changes in each section, summarised in plain text.

Section no. and name	Description of change	Brief rationale
1 Protocol synopsis 5.3 Trial rationale 8.2 Inclusion criteria 8.3 Exclusion criteria Appendix 5: Eligibility criteria	Change to inclusion criterion no. 2 to allow eligible subjects from trial LP0162-1346 to enter the extension trial. Change to exclusion criterion no. 15, reflecting that 'current participation in any other interventional clinical trial' will also be allowed for eligible subjects from trial LP0162-1346.	To also offer subjects in trial LP0162-1346 the possibility to continue treatment with tralokinumab in the extension trial.
8.3 Exclusion criteria	Change to exclusion criterion no. 9 to allow entry of subjects who during their parent trial have had a localised injection site reaction suspected to be due to hypersensitivity, provided that the subject has been able to continue IMP administrations and there has been no sign of a systemic hypersensitivity reaction.	To clarify that subjects having a localised injection site reaction suspected to be due to hypersensitivity during their parent trial are allowed to continue with IMP, both in the parent trial and extension trial, if this is considered safe. It will be at the investigator's discretion to assess if continued exposure to IMP is considered safe.

Section no. and name	Description of change	Brief rationale
8.3 Exclusion criteria	Change to exclusion criterion no. 12 to allow entry of subjects who during their parent trial have had basal cell carcinoma, localised squamous cell carcinoma of the skin, or in situ carcinoma of the cervix, provided that the subject is in remission and curative therapy has been completed.	To clarify that subjects being diagnosed with basal cell carcinoma, localised squamous cell carcinoma of the skin, or in situ carcinoma of the cervix during their parent trial are allowed to continue with IMP, both in the parent trial and extension trial. Given the nature of these malignancies, continued exposure to IMP is not considered to be a safety concern.
Appendix 4: Country-specific requirements	Appendix split into Appendix 4A: Japan (no other changes) and Appendix 4B: France (new appendix, see below).	
Appendix 4B: France	Country-specific requirement added for France: In France, urine pregnancy testing will be repeated every 4 weeks. From Week 16 onwards (when site visits will occur every 8 weeks), site staff will supply a pregnancy test kit for home use to female subjects of childbearing potential, who will take the pregnancy test at home 4 weeks after each site visit.	Requested by French regulatory health authorities (ANSM) during their protocol revew.
Appendix 8	New appendix added for protocol amendment history. Summary of previous amendment moved to this appendix.	To keep only the most recent amendment summary at the start of the protocol.

Amendment 3 (13-Dec-2018)

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

Overall rationale for the amendment:

The main reason for this amendment is to change exclusion criterion no. 6 to reflect that a wash-out period is not considered necessary because subjects are allowed to resume investigational medicinal product following 5 half-lives after the last administration of systemic immunosuppressive or immunomodulating drugs and/or systemic corticosteroids. Clarifications on how to handle duplicate assessments (i.e. assessments performed on the same day) between parent trial and trial LP0162-1337 have been added. In addition, the amendment includes other changes, as presented in the table below.

Note: The table below describes the changes in each section, summarised as plain text, and/or as tracked changes (text added to the protocol is written in **bold** and deleted text ~~has a line through it~~).

Section no. and name	Description of change	Brief rationale
8.3 Exclusion criteria	6. Treatment with the following medications within **5 half-lives** ~~4 weeks~~ prior to baseline: • Systemic immunosuppressive/immunomodulating drugs (for example, methotrexate, cyclosporine, azathioprine, mycophenolate-mofetil, Janus kinase inhibitors). • Systemic corticosteroids (excluding topical, **ophthalmic**, inhaled, or intranasal delivery).	During the parent trials subjects are allowed to resume investigational medicinal product following 5 half-lives after the last administration of these types of medications. A wash-out period is therefore not considered necessary.
1 Protocol synopsis Appendix 5: Eligibility criteria	• Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroids within **5 half-lives** ~~4 weeks~~ prior to baseline.	During the parent trials subjects are allowed to resume investigational medicinal product following 5 half-lives after the last administration of these types of medications. A wash-out period is therefore not considered necessary.
1 Protocol synopsis	Trial participation will include a screening period of 2 to 4 weeks ~~(including wash-out, if applicable)~~, a treatment period of approximately 1.5 to 2.5 years, and a safety follow-up period of 14 weeks (starting 2 weeks after last dose of IMP).	To clarify that the duration of screening is no longer dependent on the need for wash-out in acordance with exclusion criteria 6 and 7.

Section no. and name	Description of change	Brief rationale
4 Schedule of trial procedures	**If the screening period does not exceed a duration of 2 weeks, a single screening visit should preferably be performed combining the assessments specified for Visits 1 and 2. If the screening period exceeds a duration of 2 weeks (+7 days), the screening will consist of 2 separate visits (Visits 1 and 2).** ~~For subjects who do not require a washout, 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 4.~~	To clarify that the duration of screening is no longer dependent on the need for wash-out in acordance with exclusion criteria 6 and 7.
7.1 Overall trial design	The screening period has a duration of 2 to 4 weeks and includes 1 or 2 screening visits **(Visits 1 and 2)**. ~~The exact duration of the screening period for the individual subject depends on the length of any washout period needed, as specified in the exclusion criteria in Section 8.3 (that is, 4 weeks prior to Week 0 [hereinafter 'baseline'] for systemic immunosuppressive or immunomodulating drugs, systemic corticosteroid use; and 2 weeks prior to baseline for topical phosphodiesterase 4 [PDE-4] inhibitors).If no washout or a 2-week washout period is required, screening will be reduced to 2 weeks and 1 visit (Week -2; visit 2), that is, the 2 screening visits will be merged.~~ **If the screening period does not exceed a duration of 2 weeks, a single screening visit should preferably be performed combining the assessments specified for Visits 1 and 2 in the schedule of procedures in Panel 2. If the screening period exceeds a duration of 2 weeks (+ 7 days), the screening will consist of 2 separate visits (Visits 1 and 2 in the schedule of procedures in Panel 2).** Eligibility will be	To clarify that the duration of screening is no longer dependent on the need for wash-out in acordance with exclusion criteria 6 and 7.

Section no. and name	Description of change	Brief rationale
	assessed at the (first) screening visit and at baseline prior to start of treatment. **Should the screening exceed a duration of 4 weeks, the sponsor should be consulted and approval sought before the subject can attend Visit 3 (baseline visit).**	

Section no. and name	Description of change	Brief rationale
4 Schedule of trial procedures Section 11.1 Overview	If screening/baseline visits are performed on the same day as visit(s) in the parent trial, the order of assessments should be adhered to, working in parallel for both protocols. Assessments where data are captured in different vendor systems databases (ECG, ePRO and laboratory tests) need to be completed twice. In such cases, the parent trial assessment should be performed first, followed by the trial LP0162-1337 assessment.	To clarify how to handle assessments performed on the same day between parent trial and trial LP0162-1337, and to avoid duplicate assessments when possible.
8.4 Screening and screening failures 9.2 Administration of IMP	Once informed consent is obtained, a unique subject identification number (subject ID) will be assigned by enrolling the subject through the EDC system. The subject ID consists of 5 digits, the first 3 of which refer to the site number, the latter 2 are sequential numbers, starting from 01.	To clarify that entry of subject number must be done by trial staff using the EDC system rather than by interactive response technology.
4 Schedule of trial procedures 9.2 Administration of IMP	**If the subject and/or the caregiver is/are health care professional(s), no training is required, but the subject should be trained in how to handle the IMP according to the IMP handling manual, and in the procedures to be followed in the event of an emergency.**	Subjects and/or caregivers who are health care professionals are considered sufficiently qualified for performing subcutaneous injections and do not need training on this, but should receive training in handling the IMP and procedures to be followed in the event of an emergency.

Section no. and name	Description of change	Brief rationale
8.1 Subject eligibility	**It is assumed that subjects entering into this trial will in the investigator's opinion have the potential to gain therapeutic benefit from treatment with tralokinumab irrespectively of whether the subject received tralokinumab or placebo in the parent trial.** ~~It is assumed that the majority of the subjects entering into this trial will in the investigator's opinion have gained therapeutic benefit from tralokinumab in the parent trial.~~	To clarify that also subjects receiving placebo in the parent trial are expected to benefit from treatment with tralokinumab in trial LP0162-1337.
Appendix 4A Japan	Section 9.8.5 Trial product destruction **Used syringes will be destroyed at the trial site provided the trial site has procedures in place for such IMP destruction. Trial sites that do not have such IMP destruction procedures in place will dispose used IMP in sharps bins that will be shipped to the CMO.** **In Japan, used syringes will be destroyed at the trial sites.** Section 9.10 Reporting product complaints In Japan, product complaints must be reported to Pharmacovigilance at LEO K.K. using the contact information below: Fax number: +81 3 4243 3311 E-mail address: clinical_trial_jp@leo-pharma.com ~~Note: reports sent to the above fax number and email address will automatically be forwarded to Global Pharmacovigilance, LEO.~~	To clarify that used syringes will be destroyed at the trial site in Japan As the description of an internal procedure is not considered of relevance for the investigator

Section no. and name	Description of change	Brief rationale
	Section 11.1 – Order of assessments **In Japan, the order of assessments may be changed after the baseline visit to perform safety and laboratory assessments before the investigator assessments but after the PROs. The assessments must be performed in the same order for all subjects at the site.**	As the standard clinical procedure in Japan is to perform safety and laboratory assessments before subjects meet the principal investigator, a country-specific requirement has been added to allow this change in the order of assessments after the baseline visit.
	In Japan, investigators must be dermatologists or allergists.	As adolescents with atopic dermatitis in Japan are seen by dermatologists and allergists, the country-specific requirement for Japan, that the investigator must only be a dermatologist has been changed to include allergists.
	Section 13.4.1 Investigator reporting responsitbilities In Japan, SAEs must be reported to Pharmacovigilance at LEO K.K. using the contact information below: Fax number: +81 3 4243 3311 E-mail address: clinical_trial_jp@leo-pharma.com ~~Note: reports sent to the above fax number and email address will automatically be forwarded to Global Pharmacovigilance, LEO.~~	As the description of an internal procedure is not considered of relevance for the investigator
	Section 13.5 Expedited reporting of pregnancy In Japan, any pregnancy must be reported to Pharmacovigilance at LEO K.K. using the contact information below:	As the description of an internal procedure is not considered of relevance for the investigator

Section no. and name	Description of change	Brief rationale
	Fax number: +81 3 4243 3311 E-mail address: clinical_trial_jp@leo-pharma.com ~~Note: reports sent to the above fax number and email address will automatically be forwarded to Global Pharmacovigilance, LEO.~~	
Throughout	Global ~~Pharmacovigilance~~ **Safety** at LEO.	The Global Pharmacovigilance department at LEO has changed name.
Throughout	Minor editorial revisions.	Minor, and are therefore not summarised.

Amendment 4 (28-May-2019)

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

Overall rationale for the amendment:

The main reason for this amendment is to introduce the option to take skin biopsy samples at selected sites in the subgroup of subjects who had skin biopsy samples in the parent trial LP0162-1325 and to consolidate the 2 screening visits to 1 visit. In addition, the amendment includes other changes, as presented in the table below.

Note: the table below describes the changes in each section, summarised as plain text, and/or as tracked changes (text added to the protocol is written in **bold** and deleted text ~~has a line through it~~).

Section no. and name	Description of change	Brief rationale
4 Schedule of trial procedures 11.6 Skin biopsies (subgroup of subjects at selected sites) 11.9 Storage of biological samples Appendix 3B	Introduction of the option at selected sites to take 2 skin biopsy samples at Week 48 in the subgroup of subjects who had skin biopsy samples in the parent trial LP0162-1325.	To investigate the molecular profile in the skin of AD patients treated for more than 1 year with tralokinumab and to document the long-term disease control of tralokinumab.
1 Protocol synopsis 3 Schematic of trial design 4 Schedule of trial procedures 7.1 Overall trial design	Consolidation of the 2 screening visits.	As it is not necessary to perform 2 screening visits in this extension trial.

Section no. and name	Description of change	Brief rationale
8.3 Exclusion criteria	Exclusion criterion 28: 28. Any abnormal finding which in the opinion of the investigator may: • Put the subject at risk because of their participation in the trial. • Influence the results of the trial. Influence the subject's ability to complete the trial. The abnormal finding must be clinically significant and observed during the screening period. Examples include abnormal findings in physical examination, vital signs, electrocardiogram (ECG **[based on the central ECG evaluation report]**), haematology, clinical chemistry, or urinalysis **(based on results provided by the central laboratory)**.	To clarify that the investigator's evaluations of abnormal ECG and laboratory testing results during the screening period are based on reports prepared by a central ECG service company and a central laboratory, respectively.
9.6 Concomitant medication and concurrent procedures	Any medication (except for **IMP/NIMP including momethasone furoate, CYP cocktail, and vaccine received in the treatment periods in the parent trials**)~~tralokinumab/placebo) for vaccine~~ that the subject receives from 3 months prior to screening through the safety follow-up, including any of the permitted concomitant medications specified below, must be recorded in the subject's medical record and the eCRF along with details such as:	To incorporate information on trial medications the subject received in the parent trial.
9.7 Prohibited medication and procedures	Prohibited medication and procedures from baseline through safety follow-up are presented in text format rather than in tabular format.	To make the guidance on prohibited medications during the different periods of the trial more clear.

Section no. and name	Description of change	Brief rationale
Appendix 4A: Japan	In Japan, investigators must be dermatologists ~~or allergists~~.	The country-specific requirement for investigators in Japan should only include dermatologists.
Throughout	Minor editorial revisions.	Minor, and are therefore not summarised.

Amendment 5 (24-Jun-2019)

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

Overall rationale for the amendment:

The main reason for this amendment is to correct an error in the schedule of trial procedures introduced with amendment 4.

Note: the table below describes the changes in each section, summarised as plain text, and/or as tracked changes (text added to the protocol is written in **bold** and deleted text ~~has a line through it~~).

Section number and name	Description of change	Brief rationale
4 Schedule of trial procedures	Specification that the Worst Weekly Pruritus numeric rating scale, Eczema-related Sleep numeric rating scale, and Patient use of topical treatment must be performed at screening.	Correction of error introduced with protocol amendment 4.
Appendix 7 Contact list	LEO Pharma K.K. **1-105 Kanda-Jinbocho**~~3-11-6~~PPD Chiyoda-ku Tokyo 101-00**51**~~32~~ Japan	As the LEO Pharma K.K. office will move to a new location as of 01-Jul-2019.

Amendment 6 (17-Feb-2020)

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

As protocol version 7.0 was made obsolete prior to the effective date, this amendment provides an overview of the changes made from protocol version 6.0 to protocol version 8.0.

Overall rationale for the amendment:

The main reason for the amendment is to introduce the possibility for eligible subjects in selected countries of trial LP0162-1334 with adolescent subjects to continue in this long-term extension trial (LP0162-1337, ECZTEND). The purpose is to obtain long-term safety data for adolescent subjects with atopic dermatitis (AD) treated with tralokinumab.

Additional changes included in the amendment are also presented in the table below. The table below describes the changes in each section, summarised as plain text, and/or as tracked changes (text added to the protocol is written in bold and deleted text ~~has a line through it~~).

Section number and name	Description of change	Brief rationale
General changes in whole document	• **Female subjects** replaces ~~women~~. • **LP0162-1334** added to the list of parent trials (also in inclusion criterion 2 and exclusion criterion 15). • **Legal representative(s)** or **parent/guardian** or **caregiver** added to the text when relevant. • Specified when text only applies to adult subjects and/or adolescent subjects.	Updated to reflect the inclusion of subjects from the parent trial LP0162-1334 in ECZTEND.
1 Protocol synopsis 7.2 Number of subjects tested 14.1 Sample size	Subject number estimate has been updated to approximately 1,500 subjects.	Updated to reflect the expected total number of subjects to be enrolled in ECZTEND.
1 Protocol synopsis 3 Schematic of trial design	The trial design figure has been updated to include the parent trial LP0162-1334 and the updated subject number estimate of approximately 1,500 in ECZTEND. Formatting updates has also been performed.	Updated to reflect the inclusion of subjects from the parent trial LP0162-1334 in ECZTEND.
4 Schedule of trial procedures 5.5 Ethical considerations 7.1 Overall trial design 8.2 Inclusion criteria 8.4 Screening and screening failures Appendix 5 Eligibility criteria	Inclusion criterion 1 has been updated with the informed consent procedure for adolescent subjects: 1. Signed and dated informed consent has been obtained prior to any protocol-related procedures. **Signed and dated informed consent for adolescent subjects must be provided by the subject's legal representative(s) and by the subject in the form of a signed and dated informed assent (as applicable according to national laws or regulations).** This change in inclusion criterion 1 has been added to all relevant sections in the protocol. It has further been added at relevant sections that **adolescent subjects who become adults during participation in ECZTEND must re-consent by signing the informed consent form for adult subjects.**	Updated to reflect the inclusion of adolescent subjects in ECZTEND.

Section number and name	Description of change	Brief rationale
Appendix 3B Informed consent process	The adolescents informed consent process has been included and elaborated in Appendix 3B Informed consent process.	
8.2 Inclusion criteria	Inclusion criterion 6 has been updated with additional details related to adolescent subjects: Female subjects of childbearing potential **(defined as Tanner stage ≥3 or menarche)*** must use a highly effective** form of birth control (confirmed by the investigator) continuously for at least 1 month prior to the pregnancy test at baseline (Week 0), throughout the trial, and for at least 16 weeks (5 half lives of the IMP) after the last administration of IMP. * A female subject is defined as not being of childbearing 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). • **Premenarchal or have a confirmed clinical history of sterility (e.g. the subject is without a uterus or has tubal ligation).**	Updated to reflect the inclusion of adolescent subjects in ECZTEND.
1 Protocol synopsis 6 Trial objectives and endpoints 14.3.4 Primary endpoint	The primary endpoint has been updated from: ~~Number of adverse events from baseline through the last treatment visit (that is, up to Week 142).~~ The primary endpoint has been updated to: **Number of adverse events during the treatment period from baseline up to Week 142.**	To clarify that the primary endpoint in ECZTEND is the number of adverse events reported during the entire exposure period (planned to include 2 weeks [±3 days] after last dose of IMP).
1 Protocol synopsis 8.3 Exclusion criteria Appendix 5 Eligibility criteria	Exclusion criterion 2 has been updated: More than ~~20~~ **26** weeks have elapsed* since the subject received the last IMP injection in the parent trial. *To be assessed on the first day of IMP administration (baseline). Exclusion criterion 20 has been updated:	Updated to provide all subjects from the parent trial LP0162-1334 the opportunity to be enrolled in ECZTEND if eligible.

Section number and name	Description of change	Brief rationale
	History of **subject or subjects's legal representative(s) of** chronic alcohol or drug abuse within 12 months prior to screening, or any condition **(e.g., psychotic state, language barrier or other)** associated with poor compliance, as judged by the investigator.	Updated to reflect the inclusion of adolescent subjects in ECZTEND.
1 Protocol synopsis 5.4 Justification for dose 7.1 Overall trial design 9.2 Administration of IMP	Dosing regimen. The following differences between the dosing regimens for subjects from the parent trial LP0162-1334 and the rest of the subjects in ECZTEND has been specified in all relevant sections: • Tralokinumab dose for adult subjects from all parent trials, except the parent trial LP0162-1334: 600 mg initial loading dose, then 300 mg every second week. • Tralokinumab dose for subjects from the parent trial LP0162-1334*: 300 mg every second week. * All subjects from the parent trial LP0162-1334, independent of the subject's age when enrolled in ECZTEND. The justification for the dosing regimen for subjects from the parent trial LP0162-1334 has been elaborated in Section 5.4 Justification for dose.	Updated as there are no safety data available for the administration of a loading dose of 600 mg tralokinumab to adolescent subjects who are already at steady-state after treatment with 300 mg tralokinumab Q2W. Based on the LP0162-1334 trial design, it is anticipated that most of the subjects have been treated with 300 mg tralokinumab Q2W prior to enrolment in ECZTEND, and these subjects should not be unnecessarily exposed to an initial loading dose of 600 mg tralokinumab.
4 Schedule of trial procedures 6 Trial objectives and endpoints 11.1 Overview 11.3.2 Patient-reported	Update of description of the assessment and analysis of the following patient-reported outcomes: Dermatology Life Quality Index (DLQI)/Children's Dermatology Life Quality Index (CDLQI): Adult subjects from all parent trials, except the parent trial LP0162-1334, will perform the DLQI. All subjects from the parent trial LP0162-1334, independent of the subject's age during participation in ECZTEND, will perform the CDLQI.	Updated to reflect inclusion of adolescent subjects in ECZTEND as follows. In order to analyse change from parent trial baseline to the end of treatment visit in ECZTEND, subjects from the parent trial LP0162-1334 must continue the CDLQI during participation in ECZTEND.

Section number and name	Description of change	Brief rationale
outcomes (efficacy assessments) 14.3.7 Patient-reported outcomes (statistical methodology) 12 Scientific rationale for trial design and appropriateness of assessments Appendix 4A Country-specific requirements, Japan 15 References	<u>EuroQoL 5-Dimension Health Questionnaire 5 (EQ-5D-5L):</u> Subjects from the parent trial LP0162-1334 will not perfom the EQ-5D-5L. <u>Worst Weekly Pruritus numeric rating scale (NRS) and the Eczema-related NRS</u>: Subjects from the parent trial LP0162-1334 will perform an adolescent's pruritis NRS with a recall period of past 7 days and an eczema-related sleep NRS with a recall period over the past 7 nights, independent of the age of the subject during participation in ECZTEND.	In order to provide wordings tailored to adolescent subjects, subjects from the parent trial LP0162-1334 will perform an adolescent's pruritis NRS with a recall period of past 7 days, and an eczema-related sleep NRS with a recall period over the past 7 nights. Subjects from the parent trial LP0162-1334 will not perfom the EQ-5D-5L, as this questionnaire has not been validated for adolescents.
4 Schedule of trial procedures	An additional weight assessment and treatment compliance assessment at the end of treatment (EOT) visit have been added. An additional weight assessment at the early termination visit has been added.	Updated to ensure that all subjects have a weight assessment and a treatment compliance assessment at the end of their treatment period.
8.4 Screening and screening failures 10.2.2 Reasons for withdrawal from the trial 11.8 End of trial	Added reason for screening failure/withdrawal from trial, and added reason for not completing the trial or attending the safety follow-up visit: • **Withdrawal by parent/guardian.*** ***For adolescent subjects as applicable.**	Updated to reflect inclusion of adolescent subjects in ECZTEND.
9.7 Prohibited medication and procedures	The text in the section about prohibited medication and procedures has been optimised.	To clarify the section of prohibited medications in the protocol in relation to rescue medications.

Section number and name	Description of change	Brief rationale
11.2.2 Medical history	Any ongoing AEs from parent trial. **In addition, AEs reported after completion of the parent trial and prior to signing the informed consent form in the present trial must be recorded as medical history**.	To clarify the reporting of AEs with onset after completion of parent trial and before consenting to participation in ECZTEND.
11.4.5.2 Urinary pregnancy test	Added to description of pregnancy test: **For female subjects who become of childbearing potential during the trial (defined as Tanner stage ≥3 [Marshall 1969] or menarche), the investigator must reassess whether contraceptive measures are in place (if applicable), and perform the pregnancy tests according to the schedule of trial procedures (Section 4).**	Updated to reflect the inclusion of adolescent subjects in ECZTEND.
11.7 Estimate of total blood volume collected	For the longest estimated trial participation, the blood volume **drawn** will be approximately 265 mL **for adult subjects**, which is less than the volume of blood drawn during a blood donation (approximately 500 mL). **For adolescents, the total amount of blood drawn during the trial will be approximately 130 mL. The volume of blood drawn at any visit during the trial will be approximately 20 mL for all subjects. The maximum possible blood volume drawn at one visit is less than 1% of the total blood volume, and the maximum possible blood volume drawn within 4 weeks is less than 3% of the total blood volume, as recommended for the age group 0–18 years (European Commission 2008).**	To clarify that the blood volume drawn in ECZTEND is appropriate for adolescent subjects.
13.2 Collection of adverse event reports	Added sentence: **for subjects without a safety follow-up visit in the parent trial, any AE with onset before the baseline visit in ECZTEND should be reported as an AE in the parent trial.** Added sentence: **AEs with onset after the final visit in the parent trial and after informed consent has been obtained for the present trial should be recorded as an AE in ECZTEND.**	To clarify the reporting of AEs prior to treatment in ECZTEND (in accordance with the current text in Section 7.1).

Section number and name	Description of change	Brief rationale
13.4 Reporting of serious adverse events	Added sentence: **On the SAE form in the present extension trial, information regarding the subject's ID and parent trial ID must also be provided.**	To clarify that the subject's details from the parent trial are also needed on the SAE form.
13.7 Follow-up for final outcome of adverse events Appendix 2 Classification of adverse events	For SAEs which have stabilised and from which the subject cannot be expected to recover during the trial or the safety follow-up periods, **for example chronic or stabilised conditions, the final outcome at the investigator's discretion should be reported as 'recovering/resolving' or 'not recovered/not resolved'**.	To provide clarification on how to handle SAEs where the final outcome is recovering/resolving at the end of the trial.
14.3.8.1 Adverse events (statistical methodology)	An overall summary of the number of AEs, the rate of AEs (number of AEs per 100 patient-years of exposure), the number (percentage) of subjects with any treatment-emergent AEs, deaths, SAEs, withdrawals from the trial due to AEs, treatment-related AEs, and severe AEs will be presented. **The above summaries will also be made separately for subjects who transferred from the parent trial LP0162-1334.**	Updated to clarify the statistical analyses after inclusion of the parent trial LP0162-1334 in ECZTEND.
Appendix 4 Country-specific requirements	Added introduction: **This appendix describes requirements and procedures that are specific for Japan (Appendix 4A) and France (Appendix 4B). For each section, the text from the protocol is presented in normal font. The specific requirements or procedures for Japan or France are presented below in bold font.**	Added for information.
Throughout	Minor editorial revisions.	Minor, and are therefore not summarised.

Amendment 7 (25-Nov-2020)

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

Overall rationale for the amendment:

The main reason for this amendment is to extend the collection of long-term safety data for tralokinumab up to 5 years, and at the same time provide subjects the possibility to continue treatment until treatment with tralokinumab is also available to patients outside the clinical trial setting. Subjects from the parent trial LP0162-1334 will have the opportunity to continue for an additional 1-year extension, providing an additional year of safety data for adolescents/young adults. To reduce the burden of frequent site visits for subjects, the amendment will introduce a visit schedule more similar to standard practice for home use. The modified design reduces the number of site visits and instead introduces a mandatory telephone visit in between site visits to ensure close safety monitoring of the subjects.

This amendment also introduces the possibility for eligible subjects from 2 new parent trials, LP0162-1343 and TRA-WEI-0015-I, to participate in this long-term extension trial.

The table below describes the changes in each section, summarised as plain text, and/or as tracked changes (text added to the protocol is written in bold and deleted text ~~has a line through it~~).

Section number and name	Description of change	Brief rationale
Whole document	• 2 new parent trials have been added to protocol version 10 in all relevant sections: LP0162-1343 and TRA-WEI-0015-I (investigator-initiated trial). • The treatment extension and the modified trial design have been included in all relevant sections. • Trial visits have been specified to be either site visits or telephone visits in all relevant sections.	To extend the collection of long-term safety data in adult (up to 5 years) and adolescent subjects, as well as to enable continued treatment of subjects until treatment with tralokinumab is also available to patients outside the clinical trial setting (including subjects from 2 new parent trials LP0162-1343 and TRA-WEI-0015-I).
1 Protocol synopsis	Updated according to the changes in the main document (see the change descriptions below). Changes were made to the paragraphs regarding the primary endpoint, the secondary endpoints, final collection of	To reflect changes in the main document.

Section number and name	Description of change	Brief rationale
	data for the primary endpoint, trial design description including trial design panel, main criteria for inclusion, main criteria for exclusion, duration of treatment, number of subjects, and number and distribution of trial sites.	
3 Schematic of trial design	Addition of Panel 1 to provide an overview of the different scenarios for participation introduced with protocol version 10. Addition of explanatory text to introduce the 3 panels, and a reference to guidance for next steps in the case of COVID-19 pandemic restrictions.	To give trial personnel an overview of the different scenarios for trial participation introduced.
3 Schematic of trial design	The trial design figure has been modified to reflect the visit schedule until end of May 2021 and after May 2021, as well as to include the parent trials LP0162-1343 and TRA-WEI-0015-I: • Panel 2, top: Visit schedule applicable until end of May 2021: The trial design is unchanged for all subjects until end of May 2021, and for subjects who do NOT re-consent to participate after May 2021. • Panel 2, bottom: New visit schedule applicable after May 2021, for subjects who consent to participate in the trial after May 2021: The trial design has been updated to reflect the alternating site and telephone visits, the extended duration of the trial, as well as the shortened safety follow-up period, except for subjects from the parent trial LP0162-1334, who will continue to have a safety follow-up visit 16 weeks after the last dose of IMP. In addition, the timing of the visits and assessments have been updated.	The trial design has been modified after May 2021 to reduce the burden of frequent site visits, by implementing a visit schedule more similar to standard practice for home use. As tralokinumab has been shown to be well-tolerated with a favorable safety profile in the clinical development programme, a shortened safety follow-up period has been introduced for adult subjects.
4 Schedule of trial procedures	The schedule of trial procedures has been split into 2 sections: • New Section 4.1: Schedule of trial procedures applicable until end of May 2021 (Panel 3 and Panel 4). The trial procedures are unchanged, and	Schedule split in 2 to give trial personnel an easy access to the trial procedures applicable to a subject. The trial procedures have been modified to reduce the burden of

Section number and name	Description of change	Brief rationale
	applicable for all subjects until end of May 2021, and for subjects who do NOT re-consent to participate after May 2021. • New Section 4.2: New schedule of trial procedures applicable for subjects who consent to participate in the trial after May 2021 (Panel 5). The trial design has been updated to reflect the alternating site and telephone visits, the extended duration of the trial, as well as the shortened safety follow-up period, except for subjects from the parent trial LP0162-1334, who will continue to have a safety follow-up visit 16 weeks after the last dose of IMP. In addition, timing of the visits and assessments have been updated. • After May 2021, the frequency of urine dipstick analysis has been reduced, and a urine sample will only be sent to the central laboratory to perform urinalysis, if considered required by the investigator based on the urine dipstick results. A reference to guidance in case of COVID-19 pandemic restrictions have been added to this Section.	frequent site visits by implementing a visit schedule more similar to standard practice for home use. As tralokinumab has been shown to be well-tolerated with a favorable safety profile in the clinical development programme, a shortened safety follow-up period has been introduced for adult subjects. As tralokinumab has been shown to be well-tolerated with no safety concerns in relation to urinalysis, a reduced collection of urine samples has been included to reflect standard clinical practice for home use as well as only perform urinalysis if considered clinically relevant per investigator's discretion.
4 Schedule of trial procedures 4.1 ECZTEND – schedule of trial procedures until end of May 2021 4.2 ECZTEND – schedule of trial procedures after May 2021	The description of a safety follow-up period of 14 weeks' duration (starting 2 weeks after the last dose) has been omitted. The safety follow-up period and the timing of the safety follow-up visit have been clarified as follows: • Until end of May 2021 (Panel 4): The final safety follow-up visit will be 16 weeks after the last dose (i.e. 14 weeks after the EOT visit). • After May 2021 (Panel 5): The final safety follow-up visit will be 4 weeks after the last dose (i.e. 2 weeks after the EOT visit), except for subjects from the parent trial LP0162-1334, where the safety follow-up visit will be 16 weeks	To avoid confusion by describing a safety follow-up period of 14 weeks and a safety follow-up visit 16 weeks after the last dose. The safety follow-up period has been shortened for adult subjects, as tralokinumab has been shown to be well-tolerated with a favorable safety profile in the clinical development programme.

<table>
<tr><th>Section number and name</th><th>Description of change</th><th>Brief rationale</th></tr>
<tr><td>7.1.4 Safety follow-up period (after last IMP)</td><td>after the last dose (i.e. 14 weeks after the EOT visit).
Addition of Panel 7: Safety follow-up visit
<table><tr><th rowspan="2">Parent trial</th><th colspan="2">Safety follow-up visit</th></tr><tr><th>Subject does NOT re-consent to protocol version 10</th><th>Subject DOES re-consent or consent to protocol version 10</th></tr><tr><td>LP0162-1334</td><td>16 weeks after last dose</td><td>16 weeks after last dose</td></tr><tr><td>LP0162-1325, -1326, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I</td><td>16 weeks after last dose</td><td>4 weeks after last dose</td></tr></table></td><td></td></tr>
<tr><td>5.2 Experience with the investigational medicinal product</td><td>Experience with tralokinumab has been updated with the latest information about efficacy and safety.</td><td>To provide updated information about experience with tralokinumab.</td></tr>
<tr><td>5.5 Ethical considerations

5.6 Benefit/risk assessment</td><td>The nature and frequency of the monitoring of subjects in the different scenarios of the trial have been elaborated.</td><td>To clarify the change to the frequency of monitoring of subjects on site.</td></tr>
<tr><td>5.6 Benefit/risk assessment</td><td><u>Added information:</u>
The current COVID-19 pandemic may warrant many subjects in the ECZTEND trial to stay at home to comply with authority-issued preventive measures, which may impact subjects’ ability to attend visits at the trial site. To follow authorities’ restrictions and to safeguard the subjects in the ECZTEND trial, as well as providing continued therapy to secure the scientific integrity, the clinical trial protocol provides an opportunity for telephone visits and courier delivery of IMP and pregnancy tests to subjects in replacement of the site visits (see Appendix 3K for details).</td><td>To provide guidance in case of COVID-19 pandemic restrictions.</td></tr>
<tr><td>6 Trial objectives and endpoints</td><td>It has been clarified in footnotes to Panel 5 that some endpoints are not applicable for subjects from the parent trial TRA-WEI-0015-I.</td><td>Since data from the parent trial TRA-WEI-0015-I will not be transferred to LEO Pharma, as this is an investigator-initiated trial.</td></tr>
</table>

Section number and name	Description of change	Brief rationale
6 Trial objectives and endpoints 3 Schematic of trial design 4 Schedule of trial procedures	Primary endpoint: • Number of adverse events during the treatment period from baseline up to Week ~~142~~ **268**. Secondary endpoints: • IGA score of 0 (clear) or 1 (almost clear) at Weeks 16, 56, ~~80~~ **88,** 104, **136, 152, 184, 216**, and ~~128~~ **248** • EASI75 at Weeks 16, 56, ~~80~~ **88**, 104, **136, 152, 184, 216**, and ~~128~~ **248** Other endpoints: • Change in EASI score from baseline to Weeks 16, 56, ~~80~~ **88**, 104, **136, 152, 184, 216,** and ~~128~~ **248** • Change in SCORAD from baseline to Weeks 16, 56, ~~80~~ **88**, 104, **136, 152, 184, 216,** and ~~128~~ **248** • Change in POEM score from baseline to Weeks 16, 56, 80**-88**, 104, **128-136, 152, 184, 216**, and ~~128~~ **248** • Change in DLQI/CDLQI4 score from baseline to Weeks 16, 56, 80**-88**, 104, **128-136, 152, 184, 216**, and ~~128~~ **248** • Change in EQ-5D-5L score from baseline to Weeks 16, 56, 80**-88**, 104, **128-136, 152, 184, 216**, and ~~128~~ **248** • Worst Weekly Pruritus NRS at Weeks 16, 56, ~~80~~ **88,** 104, **136, 152, 184, 216**, and ~~128~~ **248** • Eczema-related Weekly Sleep NRS at Weeks 16, 56, ~~80~~ **88,** 104, **136, 152, 184, 216**, and ~~128~~ **248** • Use of topical treatment during the last week at Weeks 16, 56, ~~80~~ **88,** 104, **136, 152, 184, 216**, and ~~128~~ **248**	Endpoints have been updated to fit with the new schedule of site visit assessments and to ensure that all subjects can contribute to the efficacy analyses. It has further been ensured that all subjects are assessed approximately after 1, 2 and 3 years, when applicable.
7.1 Overall trial design 7.1.1 Overview	The whole section has been updated and more headers added to reflect the modified trial design after May 2021 according to protocol version 10. Section 7.1.3 The treatment period Week 0 and onwards): The section has been split	Section split was made to reflect and ease the understanding of the different trial procedures required until end of May 2021 and after May 2021. The trial design was modified to extend the collection of long-term safety data in adult (up to 5 years)

Section number and name	Description of change	Brief rationale
7.1.3 Treatment period (Week 0 and onwards) 7.1.3.1 Treatment initiation 7.1.3.2 Treatment period until end of May 2021 (all subjects) 7.1.3.3 Treatment period after May 2021 (subjects who consent to protocol version 10) 7.1.3.4 Trial visits in the treatment period	into Section 7.1.3.1 Treatment initiation, Section 7.1.3.2 Treatment period until end of May 2021 (all subjects), and Section 7.1.3.3 Treatment period after May 2021 (subjects who consent to protocol version 10). Furthermore, descriptions of the different visit types have been added in a new Section 7.1.3.4. It has been clarified in the sections that treatment will be stopped as follows: • Subjects who do NOT re-consent to continue in the trial after May 2021 will stop treatment by end of May 2021. • Subjects from the parent trial LP0162-1334 who re-consent or consent to participate in the trial after May 2021 will stop treatment by end of May 2022. • Subjects from the parent trials LP0162-1325, -1326, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I who re-consent or consent to participate in the trial after May 2021 will stop treatment at a country-specific completion date.	and adolescent subjects, as well as to enable continued treatment of subjects until treatment with tralokinumab is also available to patients outside the clinical trial setting (including subjects from 2 new parent trials LP0162-1343 and TRA-WEI-0015-I).
7.2 Number of subjects needed 14.1 Sample size	Updated to reflect the total number of subjects and sites expected after inclusion of the 2 additional parent trials LP0162-1343 and TRA-WEI-0015-I: Number of subjects: ~~1,500~~ **1,600** subjects Number of sites: ~~300~~ **330** sites.	To specify the new expected total number of subjects and sites included in the trial.
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. The trial treatment will be stopped for all subjects in all countries by 31-May-2021, and the subjects will have their final safety follow-up visit 16 weeks later. By 31-May-2021, the majority of subjects will have been exposed to tralokinumab for~~	Updated to reflect the new trial design.

Section number and name	Description of change	Brief rationale
	~~3 years (including the exposure in the parent trial), which is considered appropriate for evaluating long-term safety of~~ tralokinumab. The end of the trial is defined as the date of the last visit of the last subject in the trial globally. **By the end of this trial, subjects will have been exposed to tralokinumab for up to 5 years, which is considered appropriate for evaluating long-term safety of tralokinumab.** **The** final collection of data for the primary endpoint ~~for each subject~~ will occur ~~at Week 142~~ **by Q2 2024**. **A subject is considered to have completed the trial if the subject has completed all periods of the trial, including the safety follow-up visit, according to protocol version 10 or earlier versions.** **A subject is considered to have completed the treatment period if the subject has completed the EOT visit with no 'primary reason for withdrawal from trial'. This will be:** • **Approximately end of May 2021 for subjects completing according to protocol version 9 or earlier versions.** • **Approximately end of May 2022 for subjects from the parent trial LP0162-1334 completing according to protocol version 10.** • **At a country-specific end of treatment date (Appendix 3J) for subjects from the parent trials LP0162-1325, -1326, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I completing according to protocol version 10.**	
8 Trial population 8.2 Inclusion criteria	Inclusion criteria 2 and exclusion criteria 15: addition of the 2 new parent trials LP0162-1343 and TRA-WEI-0015-I. Inclusion criteria 6: Female subjects of childbearing potential (defined as Tanner stage ≥3 or menarche)* must use a highly effective** form of birth control (confirmed	Inclusion criteria 2 and exclusion criteria 8 and 15 updated to reflect the inclusion of subjects from the parent trials trials LP0162-1343 and TRA-WEI-0015-I.

Section number and name	Description of change	Brief rationale
8.3 Exclusion criteria	by the investigator) continuously for at least 1 month prior to the pregnancy test at baseline (Week 0), throughout the trial, and for at least 16 weeks (5 half-lives of the IMP) after the last administration of IMP. *A female subject is defined as not being of childbearing 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). • Premenarchal ~~or have a confirmed clinical history of sterility (e.g., the subject is without a uterus or has tubal litigation)~~. **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), **same-sex partner**, or vasectomised partner (given that the subject is monogamous). Exclusion criteria 7: Treatment with topical PDE-4 inhibitors **or topical JAK inhibitors** within 2 weeks prior to baseline. Exclusion criteria 8: 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 are eligible provided they are vaccinated against	Inclusion criteria 6 updated to provide more clarity. Exclusion criteria 7 updated to be consistent with available treatments options.

Section number and name	Description of change	Brief rationale
	hepatitis B and have negative HBsAg and HBcAb. ***Subjects from the parent trial LP0162-1343 with a positive HBsAb may be randomised provided they have negative HBsAg, HBcAb, and HCV serology at screening.**	
9.7 Prohibited medication and procedures	From baseline through end of treatment: • Higher potency topical corticosteroids (US class <4 or Europe class >3). Can be used as rescue for intolerable AD symptoms (see Section 9.5). • **Topical** phosphodiesterase 4 (PDE-4) inhibitors. • **Topical JAK inhibitors.** • UVA or UVB, psoralen + UVA (PUVA), other phototherapy, or tanning beds. • 3 or more bleach baths per week.	To clarify the section on prohibited medication.
9.8.3 Drug accountability	Subjects will attend ~~trial~~ **site** visits ~~at least every 8 weeks~~ **on a regular basis** (see Section 4).	To reflect the new visit schedule.
10.2.1 Stopping rules	Subjects withdrawn from the trial should complete the ~~14 week~~ safety follow-up period **as specified in Section 7.1**. **Reasons for withdrawal from the trial are described in Section 10.2.2**.	Updated to reflect the changed safety follow-up period and to make reference to Section 10.2.2.
10.2.2 Reasons for withdrawal from the trial	Subjects withdrawn from the trial ~~should~~ **must** complete the ~~14 week~~ safety follow-up period **as specified in Section 7.1.** **Stopping rules are are described in Section 10.2.1**.	Updated to reflect the changed safety follow-up period and to make reference to Section 10.2.1.
10.2.3 Reasons for temporary discontinuation of IMP	IMP dosing MAY be temporarily suspended in the event of: • Other intercurrent illness or major surgery. • An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents. **IMP dosing SHOULD be temporarily suspended in the event of:**	To provide clarity on when IMP may and should be temporarily discontinued, or must be withdrawn.

Section number and name	Description of change	Brief rationale
	• Treatment with systemic corticosteroids or non-steroidal immunosuppressive/immunomodulating medications (for example, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, Janus kinase inhibitors, dupilumab, or other biologics). If any of the stopping rules are met (see Section 10.2.1) **or any of the withdrawal reasons are met (Section 10.2.2)**, the subject must be withdrawn from the trial.	
10.3 Early termination assessment	Added sentence: **An EOT (end of treatment) form and an end of trial form must be completed as specified in Section 11.8.**	To avoid misunderstandings.
11.4.2 Vital signs	Vital signs will be measured in a supine **or sitting** position…. Should the repeated measurement result in a normal value, the measurement must be repeated ~~once more~~ **approximately 15 minutes after the second measurement with subjects resting in a supine or sitting position**.	To clarify how vital signs are to be measured.
11.4.5.1 Overview	Footnotes updated to Panel 13: [3] Urine samples will be tested at the trial site (dipstick). **Until end of May 2021**, in case of abnormal dipstick results, a urine sample will be sent to the central laboratory for microscopic examination (leucocytes, erythrocytes, and casts). **After May 2021, a urine sample will only be sent to the central laboratory to perform urinalysis if considered required by the investigator based on the urine dipstick results.** [4] Measured at screening only. **In case additional analysis are needed to support the interpretation of the initial test results for hepatitis B, hepatitis C, or HIV, these will be performed by the central laboratory as applicable**.	As tralokinumab has been shown to be well-tolerated with no safety concerns in relation to urinalysis, a reduced collection of urine samples has been included to reflect standard clinical practice for home use as well as only perform urinalysis if considered clinically relevant per investigator's discretion.

Section number and name	Description of change	Brief rationale
11.4.5.2 Urine pregnancy test	The test will be repeated at Week 4 and thereafter ~~at all site visits~~ **the schedule of pregnancy testing is** as shown in the schedule of trial procedures (Section 4). ~~The date and the outcome of~~**After May 2021, subjects must in addition to the test performed at the trial site, perform** the urine pregnancy test **at home within 48 hours before the telephone visit using the kit supplied by the site staff. The subject** will **also** be ~~recorded~~ **provided with a urine pregnancy test instruction (pictogram). The result of the pregnancy test should be communicated to the site during the telephone visit and documented** in the eCRF ~~('positive', 'negative')~~ **and source documents**.	To ensure the pregnancy test is performed at regular intervals despite the longer time period between site visits after end of May 2021.
11.7 Estimate of total blood volume collected	The total volume of blood to be drawn for each subject will depend on the time of their entry into the trial and the **local** duration of the trial (Appendix 3J). For **adult subjects,** the ~~longest estimated trial participation, the~~ **total** blood volume drawn will be approximately 265 mL ~~for adult subjects,~~ **until end of May 2021, plus 70 mL per year of trial participation after May 2021**~~which is less than the volume of blood drawn during a blood donation (approximately 500 mL)~~. For adolescents, the total amount of blood drawn ~~during the trial~~ **until end of May 2021** will be approximately ~~130 mL.~~**240 mL, plus 70 mL for the 1 year extension until end of May 2022**.	Changed to reflect the extended trial period and the changed blood drawing schedule.

Section number and name	Description of change	Brief rationale
12 Scientific rationale for trial design and appropriateness of assessments	Added text: **The trial design has been modified with protocol version 10 to secure long term safety data of up to 5 years globally. The treatment extension for subjects from the parent trials LP0162-1325, -1326, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I will be country-specific to allow for treatment with tralokinumab until tralokinumab is available to patients outside the clinical trial setting (Appendix 3J). Subjects from the ongoing adolescent parent trial LP0162-1334 are offered a total treatment extension of 1 year until end of May 2022.** **The trial design has been modified to decrease the burden of frequent site visits for subjects by introducing a visit schedule more similar to standard practice for home use. To ensure close safety monitoring throughout the treatment period, a mandatory telephone visit will be performed in between site visits.**	To clarify the rationale for extending treatment and reducing the frequency of site visits.
13.4.2 LEO Pharma reporting responsibilities	For the IMP, the Investigator's Brochure, edition ~~17~~ **19** and subsequent updates must be used.	Updated to newest edition.
13.6.3 Medication error	Broadly, medication errors fall into 4 categories: wrong medication, wrong dose (including strength, form, concentration, amount**, as well as administration with an interval of less than 7 days),** wrong route of administration, or wrong subject.	To clarify the definition of a medication error.
14.2 Trial analysis sets	Added text: **Data from the investigator-initiated parent trial TRA-WEI-0015-I will not be transferred to LEO Pharma. Thus, endpoints defined as change from baseline (in parent trial) will not be calculated for subjects from this trial,**	To clarify to what extent data from the parent trial TRA-WEI-0015-I will be included in endpoints and summarised data presentations.

Section number and name	Description of change	Brief rationale
	and data from this trial will not be included in tables summarising endpoints defined as change from baseline or where data are presented by responder/non-responder. Subjects from this parent trial will be contributing to the primary endpoint and included in summary tables where possible.	
14.3.4 Primary endpoint	The primary endpoint in this trial is number of adverse events during the treatment period from baseline up to Week ~~142~~ **268,** and the analysis of this is covered in Section 14.3.8.	To reflect the extended treatment period.
14.3.6 Other endpoints	An analysis has been added: **As the frequency of site visits is reduced after May 2021, a sensitivity analysis excluding data captured after May 2021 will be performed for the 'proportion of time' endpoints.**	Sensitivity analysis added as the less frequent assessment of efficacy after May 2021 could influence the estimation and precision of the 'proportion of time' endpoints.
14.3.7 Patient-reported outcomes	Added text: **In the special case where a subject has an assessment at both Week 80 and Week 88, the Week 80 assessment (corresponding to approximately 1½ years) will be used for the Week 80-88 endpoint evaluation. Likewise, the Week 128 assessment (~ 2½ years) will be prioritised for the Week 128-136 endpoint evaluation.** **Changes from baseline will not be presented for subjects from the parent trial TRA-WEI-0015-I, since data from this investigator-initiated trial will not be transferred to LEO Pharma (see Section 14.2).**	To clarify the handling of the Week 80-88 and Week 128-136 endpoints. To clarify that data from the parent trial TRA-WEI-0015-I will not be included in change from baseline endpoints for patient-reported outcomes.
14.3.8.1 Adverse events	An additional AE summary has been added, and some tabulations deleted: **As the frequency of site visits is reduced after May 2021, an additional overall AE summary table will be presented that excludes events and exposure time after May 2021.** The severity ~~for each type of AE will be tabulated. Where there are several~~	To evaluate the event rate of AEs prior to modification of the site visit frequency. Tabulations deleted as not possible to perform.

Section number and name	Description of change	Brief rationale
	~~recordings of severity for a given type of AE, severity will be taken as the most severe recording for that AE. The~~ **and** causal relationship to IMP for each type of AE will be tabulated. ~~Where there are several recordings of causal relationship to the IMP for a given type of AE, causal relationship will be taken as the most related recording from the last report of that AE, since that is when the investigator will be in possession of most information and so best able to judge causal relationship.~~	
14.3.10 Interim analysis	~~To support submission for marketing approval~~, Interim evaluation and reporting of ~~selected~~ trial data (~~for example, baseline demographies, disease characteristics, and SAEs)~~ will be ~~performed~~ **perfomed (e.g. to support submissions for marketing approval or sharing of results at conferences).**	To clarify the interim evaluation.
Appendix 3B: Informed consent process	Added text: **To participate in the ECZTEND trial after May 2021, subjects must re-consent/consent to protocol version 10.**	To clarify that continuing in ECZTEND after May 2021 requires the subject or subject's legal representative to sign the new version of informed consent.
Appendix 3E: Registration, reporting, and publication policy	Results of this clinical trial will be posted on the LEO Pharma corporate website in accordance with LEO Pharma's ~~Position on Public Access to Clinical Trial Information~~ **position on public access to clinical trial information** no later than ~~12~~ **6** months after trial completion.	To reflect that the trial includes adolescent subjects.
Appendix 3J: Country-specific end of treatment date	New appendix with country-specific treatment end dates for subjects from the parent trials LP0162-1325, -1326, -1339, -1341, -1342, -1343, -1346, and TRA-WEI-0015-I.	The end of treatment date is country-specific to allow for treatment until treatment with tralokinumab is also available to patients outside the clinical trial setting, except for subjects from the parent trial LP0162-1334, who will end treatment by end of May 2022 in all countries.

<table>
<tr><th>Section number and name</th><th>Description of change</th><th>Brief rationale</th></tr>
<tr><td></td><td>
<table>
<tr><th>Country</th><th>Approximate la</th></tr>
<tr><td>US</td><td>May</td></tr>
<tr><td>Germany</td><td>Aug</td></tr>
<tr><td>UK</td><td>Jun</td></tr>
<tr><td>France</td><td>Aug</td></tr>
<tr><td>Italy</td><td>Jan</td></tr>
<tr><td>Belgium</td><td>Sep</td></tr>
<tr><td>Canada</td><td>May</td></tr>
<tr><td>Spain</td><td>Jan</td></tr>
<tr><td>Poland</td><td>May</td></tr>
<tr><td>Czech Republic</td><td>Oct</td></tr>
<tr><td>Japan</td><td>May</td></tr>
</table>
Subjects from the parent trial LP0162-1334 will end treatment by end of May 2022 in all countries.
</td><td></td></tr>
<tr><td>Appendix 3K: COVID-19</td><td>New Appendix 3K: The clinical trial addendum dated 21-Apr-2020 has been integrated as an appendix, and optimised to apply to protocol version 10. This appendix provides an opportunity for telephone visits and courier delivery of IMP and pregnancy tests to subjects that are unable to attend site visits due to COVID-19 restrictions. It further provides a modified inclusion criterion 2, which is only applicable for subjects under COVID-19 restrictions.</td><td>To ensure the possibility of continued treatment despite the local restrictions and restricted site access caused by the COVID-19 pandemic.</td></tr>
<tr><td>Appendix 4B: France</td><td>Trial specific text has been deleted so that the specific procedures for France are independent on which protocol version the subject follows.</td><td>The procedures for France are independent of the protocol version followed.</td></tr>
<tr><td>Appendix 5: Eligibility criteria</td><td><u>Inclusion criteria 2 and exclusion criteria 15:</u> added the 2 new parent trials LP0162-1343 and TRA-WEI-0015-I.
<u>Exclusion criteria 7:</u> Treatment with topical PDE-4 inhibitors or topical JAK inhibitors within 2 weeks prior to baseline.
<u>Exclusion criteria 8:</u> Positive HBsAg, HBsAb*, HBcAb, or anti-HCV serology at screening. Subjects with positive HBsAb are eligible provided they are vaccinated against hepatitis B and have negative HBsAg and HBcAb
*Subjects from the parent trial LP0162-1343 with a positive HBsAb may be randomised provided they have negative</td><td>Inclusion criteria 2 and exclusion criteria 8 and 15 updated to reflect the inclusion of subjects from the parent trials trials LP0162-1343 and TRA-WEI-0015-I.
Exclusion criteria 7 updated to be consistent with available treatments options.</td></tr>
</table>

Section number and name	Description of change	Brief rationale
	HBsAg, HBcAb, and HCV serology at screening.	
Throughout	Minor editorial revisions. The word ~~enrolled~~ has been replaced with **included** in the entire document.	Minor, and are therefore not summarised.

Amendment 8 (12-Feb-2021)

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

Overall rationale for the amendment:

The main reason for this amendment is to correct a typo in Panel 1 that provides an overview of scenarios for trial participation in protocol version 11 and to correct the estimated total amount of blood drawn in adolescent subjects.

The table below describes the changes in each section, summarised as plain text, and/or as tracked changes (deleted text ~~has a line through it~~).

Section number and name	Description of change	Brief rationale
3 Schematic of trial design	In Panel 1 that provides an overview of scenarios for trial participation in protocol version 11, the cross-reference to Section 4.2 has been corrected to Section 4.1 for subjects with last visit before end of May 2021 and who continue in the trial.	The previous cross-reference to Section 4.2 was incorrect.
11.7 Estimate of total blood volume collected	For adolescents, the total amount of blood drawn until end of May 2021 will be approximately ~~240~~ 130 mL, plus 70 mL for the 1 year extension until end of May 2022.	The previous estimated total blood volume drawn for adolescent subjects was incorrect.
Throughout	Minor editorial revisions.	Minor, have therefore not been summarised.