Clinical trial protocol

LP0190-1488

A phase 2 trial to evaluate the efficacy and safety of orally-administered LEO 152020 tablets compared with placebo tablets for up to 16 weeks of treatment in adults with moderate to severe atopic dermatitis

Phase 2 – Efficacy and safety

A randomized, triple-blind, placebo-controlled, parallel-group, international trial

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:**	**LP0190-1488**
	EudraCT no.:	**2020-004561-39**
	NCT no.:	**NCT05117060**
	Date:	**29-Mar-2022**
	Version:	**5.0 Global**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

Electronic signatures made within LEO Pharma Clinical Vault are legally binding equivalent of traditional handwritten signatures. The following persons have approved this clinical trial protocol by using electronic signatures as presented on the last page of this document:

PPD, MD
PPD, Medical Sciences

PPD, PhD
Biostatistics lead, Medical Sciences

PPD, MD
Medical lead, Medical Sciences

PPD, PhD
Clinical operations lead, Global Clinical Operations

PPD, MD
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.

Clinical trial protocol amendment summary

Document history

Document	Date	Amendment/addendum type	Protocol/addendum version
Amendment 5 (non-substantial)	29-Mar-2022	Global [a]	5.0 Global
Amendment 4 (substantial)	30-Nov-2021	Local (Germany [b])	4.0 DE
Amendment 3 (substantial)	06-Oct-2021	Global [c]	3.0 Global
Addendum 1 to amendment 1	05-Aug-2021	Local (Germany [d])	1.0 DE
Amendment 2 (non-substantial)	07-Jul-2021	Local (Czech Republic [e])	2.0 CZ
Amendment 1 (non-substantial)	30-Jun-2021	Local (Germany [f])	2.0 DE
Original protocol	12-Feb-2021	NA	1.0 Global

Abbreviations: BfArM = German Federal Institute for Drugs and Medical Devices; CZ = Czech Republic; DE = Germany; NA = not applicable.

[a] This global protocol amendment includes the changes implemented in amendment 4.

[b] Done at the request of the Ethics Committee of CCI [redacted]. This local protocol amendment took source in version 3.0 Global which was the latest version of the protocol submitted in Germany at the time the local protocol amendment was prepared.

[c] This global protocol amendment included the changes implemented in amendments 1 and 2 and in addendum 1 to amendment 1.

[d, f] Done at the request of the German Federal Institute for Drugs and Medical Devices (BfArM).

[e] Done at the request of the Czech State Institute for Drug Control.

Amendment 5 (30-Mar-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 or subsequent regulation because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

The main purpose of this protocol amendment is to:

- Revise the response scale of the Difficulty CCI [redacted] question in the eDiary following agreement with the FDA post final protocol.
- Clarify the formulation of the sleep disturbance endpoints and their analysis based on their source data and the type of response scale.

This global protocol amendment also includes the changes implemented in the local (German) protocol amendment 4 (version 4.0 DE) and will serve as global consolidated protocol for the trial going forward. For more detail about amendment 4, see Appendix 10.

The changes to the protocol are summarized in the table below. Deleted text is ~~crossed out~~ while added text is **bold**. Additional minor changes, not listed in the table, were implemented for accuracy and consistency.

Summary of changes

Section no. and name	Description of change	Brief rationale
Section 6 Trial objectives, estimands, and endpoints (under the objective related to sleep disturbance and nocturnal CCI	Exploratory endpoints **Based on eDiary data** • ~~Change in~~ Difficulty CCI ~~(weekly average) from baseline to~~ **at** Week CCI • ~~Change in~~ Frequency of CCI ~~(weekly average) from baseline to~~ **at** Week CCI • CCI **at Week** CCI • CCI **at Week** CCI **Based on actigraphy data** • Change in CCI from baseline to Week CCI • Change in CCI from baseline to Week CCI • Change in number of nocturnal CCI events per hour from baseline to Week CCI • Change in duration of nocturnal CCI per hour from baseline to Week CCI	The sleep disturbance endpoints will be based on data from both the eDiary and actigraphy devices. The response scales in the actigraphy devices are continuous while those in the eDiary are categorical. Therefore, a change from baseline does not have a clinically relevant interpretation for the eDiary data. The corresponding endpoints were therefore revised to a single measurement at Week CCI The comparison between the data at baseline and Week CCI will be described in the SAP. For clarity, the sleep disturbance endpoints were further classified according to the source data. The changes are considered non-substantial as related to exploratory endpoints with no impact on the primary nor secondary objectives of the trial.
Section 11.5.3 Difficulty CCI (eDiary)	Difficulty CCI is a single item questionnaire designed to assess the subject's difficulty CCI because of itchy skin the past night. It will be assessed on ~~an 11-point NRS with anchors at 0 'not at all difficult' and 10 'extremely difficult'~~ **a 5-point categorical scale ('not difficult', 'a little difficult', 'moderately difficult', 'extremely difficult', 'I don't know')**.	Following advice by the FDA post final protocol. The original numerical scale was replaced by a categorical scale.

Section no. and name	Description of change	Brief rationale
Section 14.3.10 Analysis of exploratory endpoints	These endpoints will be summarized descriptively by week and treatment group. ~~Similarly,~~ • ~~Change in CCI from baseline to Week CCI~~ • ~~Change in CCI from baseline to Week CCI~~ • ~~Change in Difficulty CCI weekly average) from baseline to Week CCI~~ • ~~Change in Frequency of CCI (weekly average) from baseline to Week CCI~~ ~~will be collected using eDiary. These endpoints and change in nocturnal CCI which also is collected using eDiary will be summarized descriptively by week and treatment group.~~ The weekly average of data collected using actigraphy ~~and eDiary~~ will be based on data collected over 7 days. Data collected after the initiation of rescue medication **or permanent discontinuation of IMP** will be excluded from the calculation of the weekly averages. The text deleted was revised to: **The following sleep disturbance endpoints will be collected using the eDiary and summarized descriptively by week and treatment group:** • **Difficulty CCI at Week CCI** • **Frequency of CCI at Week CCI** • **CCI at Week CCI** • **CCI at Week CCI**	Consequential to change in Section 6 Trial objectives, estimands, and endpoints (see above). To clarify the analysis of the sleep disturbance endpoints based on eDiary data and to align the analysis of actigraphy data with analyses of other endpoints. The changes are considered non-substantial as related to exploratory endpoints with no impact on the primary nor secondary objectives of the trial.
Appendix 4 Country-specific requirements (in subsection Japan)	In Section 8.2 Inclusion criteria, the note to inclusion criterion 1 was revised to: In Japan, if the subject is less than 20 years old **prior to 01-Apr-2022**, the legal representative must sign the informed consent.	To reflect that the Japanese legal age of majority will change from 20 to 18 years on 01-Apr-2022.

Section no. and name	Description of change	Brief rationale
Appendix 10 Protocol amendment history	Amendment 3 moved from Clinical trial protocol amendment summary down to Appendix 10. Amendment 4 added.	Administrative change.

Abbreviations: please refer to the list of abbreviations.

Table of contents

List of panels

List of abbreviations

AChE	acetylcholine esterase
AD	atopic dermatitis
ADSD	Atopic Dermatitis Symptom Diary
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AR(1)	autoregressive model of order 1
AS	area score
CCI	CCI
BfArM	German Federal Institute for Drugs and Medical Devices
BSA	body surface area
CCL17	chemokine (C-C motif) ligand 17
CDISC	Clinical Data Interchange Standards Consortium
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum serum concentration of IMP
CMH	Cochran-Mantel Haenszel
CMO	contract manufacturing organization
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	corona virus disease 2019
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CTP	clinical trial protocol
CTR	clinical trial report
C_{trough}	lowest IMP concentration before next dose of IMP is administered
CZ	Czech Republic

DE	Germany
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
EASI	Eczema Area and Severity Index
EASI 50	decrease in EASI of at least 50% from baseline
EASI 75	decrease in EASI of at least 75% from baseline
EASI 90	decrease in EASI of at least 90% from baseline
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EFPIA	European Federation of Pharmaceutical Industries and Associations
eGRF	estimated glomerular filtration rate
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL 5-Dimension Health Questionnaire 5 Level
FAS	full analysis set
FDA	United States Food and Drug Administration
FWER	familywise error rate
FXR	potent farnesoid X receptor
GCP	Good Clinical Practice
GPP3	Good Publication Practice 3
HADS	Hospital Anxiety and Depression Scale
HBsAg	hepatitis B surface antigen
HCP	healthcare professional
HCV	hepatitis C virus antibody
HDL	high density lipoprotein
HGM-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
H1R, H2R, H3R, H4R	histamine 1, 2, 3, or 4 receptor
ICF	informed consent form

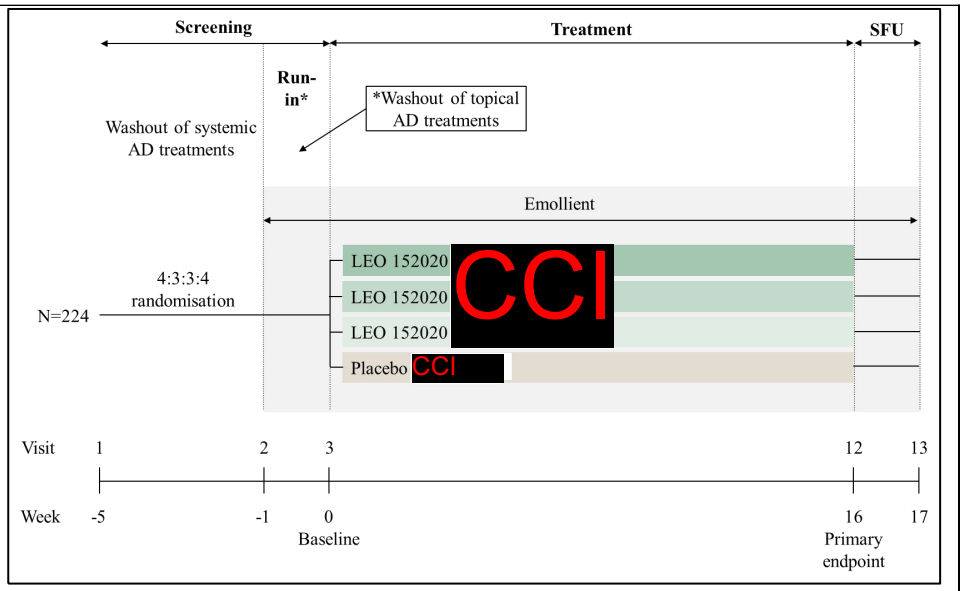
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ID	identification number
IE	intercurrent event
IEC	independent ethics committee
IFN	interferon
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IL-13	interleukin 13
IL-22	interleukin 22
IMP	investigational medicinal product
IND	investigational new drug
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JAK	Janus kinase
JM	joint model
LDL	low density lipoprotein
LEO 152020	investigational medicinal product in this trial
LS	least squares
LS-mean	least squares mean
MAR	missing at random
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
min	minimum
MMRM	mixed model for repeated measurements
MNAR	missing not at random
N	number of subjects

NA	not applicable
NBUVB	narrow-band ultraviolet B
NCT	National Clinical Trial
NOAEL	no adverse-effect level
NR	non-response
NRI	non-responder imputation
NRS	numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
PCR	polymerase chain reaction (test)
PD	pharmacodynamic(s)
PDE4i	phosphodiesterase 4 inhibitor
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
CCI	CCI
PK	pharmacokinetic(s)
PMDA	Japanese Pharmaceuticals and Medical Devices Agency
POEM	Patient-oriented Eczema Measure
PRO	patient-reported outcome
PUVA	psoralen + ultraviolet A
CCI	CCI
RADA	Rapid Actigraphy Data Analyzer (software)
SAE	serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAF	safety analysis set
SAP	statistical analysis plan
SCORAD	Scoring Atopic Dermatitis
SD	standard deviation

seq	sequencing
sIL-2R	soluble interleukin 2 receptor
SOC	system organ class
SS	severity score
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
Syk	spleen tyrosine kinase
TARC	thymus and activation-regulated chemokine
TCI	topical calcineurin inhibitor(s)
TCS	topical corticosteroid(s)
Th2	T helper type 2 cell
UVA	ultraviolet A
UVA1	ultraviolet A1
UVB	ultraviolet B
vIGA-AD	Validated Investigator Global Assessment Scale for Atopic Dermatitis
CCI	CCI
WOCF	worst observation carried forward
WPAI:AD	Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis

1 Protocol synopsis

<table>
<tr><td>Trial ID
EudraCT no.:
NCT no.:
IND no.:</td><td>LP0190-1488
2020-004561-39
NCT05117060
143394</td></tr>
<tr><td>Title of trial</td><td>A phase 2 trial to evaluate the efficacy and safety of orally-administered LEO 152020 tablets compared with placebo tablets for up to 16 weeks of treatment in adults with moderate to severe atopic dermatitis</td></tr>
<tr><td>Short title of the trial</td><td>Efficacy and safety of different dose regimens of LEO 152020 tablets for the treatment of adults with moderate to severe atopic dermatitis up to 16 weeks</td></tr>
<tr><td>Main objective(s) and endpoint(s)</td><td>
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary objective:
To explore the exposure-response relationship of LEO 152020 and evaluate efficacy of LEO 152020 compared with placebo for up to 16 weeks of treatment in subjects with moderate to severe AD</td><td>Primary endpoint:
• Change in EASI [a] from baseline to Week 16.</td></tr>
<tr><td>Secondary objective:
To evaluate the safety of LEO 152020 compared with placebo in subjects with moderate to severe AD</td><td>Secondary endpoint:
• Number of AEs from baseline to Week 16+3 days per subject.</td></tr>
</table>
Abbreviations: AD = atopic dermatitis; AE = adverse event; EASI = Eczema Area Severity Index.
[a] EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. EASI is a composite score ranging from 0 to 72 with higher scores indicating a more severe or more extensive condition.
</td></tr>
<tr><td>Final collection of data for the primary endpoint</td><td>Week 16</td></tr>
<tr><td>Trial design</td><td>The trial design is illustrated in the figure below.
The trial will consist of core assessments/procedures and optional components (wristband actigraphy, skin biopsies, and exit interviews), which are not required for participation in the core part of the trial and for which the subject will be asked to provide additional consent.
The trial will consist of:
• A screening period of maximum 5 weeks (at the earliest Week -5 to baseline) including a run-in period of 1 week (Week -1 to baseline).
• A treatment period of 16 weeks (baseline to Week 16).
• A safety follow-up period of 7 days (Week 16 to Week 17).</td></tr>
</table>



Abbreviations: AD = atopic dermatitis; N = number of subjects; SFU = safety follow-up.

Randomization will take place at baseline. The primary endpoint will be assessed at Week 16. The final safety assessments will be conducted at Week 17.

From the screening period, the subject will be asked to stop any systemic AD treatment. From the run-in period, the subject will be asked to stop any topical AD treatment with TCS, TCI, PDE4i, and/or topical JAK inhibitors and to apply an emollient (background treatment) at least twice daily. The subject will also be asked to start completing an eDiary daily.

At baseline, the subject will be randomized to 1 of 4 oral treatments as described below (Number of subjects).

In the treatment period, the subject will be asked to self-administer LEO 152020 or placebo tablets twice daily for 16 weeks. In this period, the subject will be asked to continue applying the emollient as needed and complete the eDiary. The subject will also be asked to visit the site for assessments and procedures.

In the safety follow-up period, the subject will be asked to stop treatment with LEO 152020 or placebo tablets and the safety of the treatment will further be assessed at the safety follow-up visit (Week 17).

An independent data monitoring committee will assess subject safety and overall trial conduct periodically. Based on their assessment, the committee will issue recommendations to LEO Pharma as to the pursuit of the trial.

Main assessments	• Eczema Area and Severity Index (EASI). • Adverse events.
Main criteria for inclusion	• Adult, age 18 years or older at screening. • Diagnosis of chronic atopic dermatitis (AD). • History of AD ≥1 year prior to baseline. • Recent (within 6 months prior to baseline) documented history of inadequate response to topical AD treatments or subject for whom topical AD treatments are medically inadvisable. • 7.1≤ EASI ≤50 at baseline. • vIGA-AD score ≥3 at baseline.

Main criteria for exclusion	• Previous treatment with an oral H4R antagonist (including LEO 152020) within 6 months prior to baseline. • Previous treatment with 3 or more systemic AD treatments prior to screening. • Women who are pregnant, intend to become pregnant, or are lactating.
Investigational medicinal product(s)	• Name of active IMP: LEO 152020 film-coated tablet. • Active substance: LEO 152020. • Dosage form: film-coated tablet. • Dose regimens: LEO 152020 CCI [redacted] LEO 152020 CCI [redacted] LEO 152020 CCI [redacted] • Method of administration: oral. • Name of placebo: LEO 152020 placebo film-coated tablet. • Dosage form: film-coated tablet. • Method of administration: oral.
Duration of trial participation	Up to 22 weeks: maximum 5 weeks of screening + 16 weeks of treatment + 1 week of safety follow-up
Number of subjects	At baseline, a total of 224 subjects (including 28 Japanese subjects) will be randomized in a 4:3:3:4 ratio to: • LEO 152020 CCI [redacted] • LEO 152020 CCI [redacted] • LEO 152020 CCI [redacted] • Placebo CCI [redacted].
Number and distribution of trial sites	Approximately 60 sites in Europe, North America, Japan, and Australia.
Statistical methods	Primary and secondary endpoints: A primary and 2 supplementary estimands will be defined for the primary endpoint, change in EASI from baseline to Week 16, in order to assess different clinical questions of interest. • The primary estimand for the primary endpoint will use the *hypothetical* strategy to handle the occurrence of pre-defined intercurrent events (initiation of rescue treatment and permanent discontinuation of IMP). • A first supplementary estimand will use the *treatment policy* and hypothetical strategies to account for the occurrence of intercurrent events. • A second supplementary estimand will use the *composite* and hypothetical strategies to handle the occurrence of intercurrent events. For the main analysis of the primary estimand, data observed after the occurrence of an intercurrent event will be excluded from the analysis. Missing data will be assumed to be MAR. The primary endpoint will be analyzed using an MMRM including treatment, visit, visit by treatment interaction terms, and region (Japan, non-Japanese countries) as factors, and adjusting for the baseline EASI score as a covariate. The covariance matrix will be assumed to have an unstructured form and the Kenward-Rodger approximation will be used to estimate the denominator degrees of freedom. To explore the exposure-response relationship, the change in EASI score from baseline to Week 16 will be assessed based on an ANCOVA model including region as a factor and C_{trough} at Week 16 and baseline EASI score as covariates. Data observed after the occurrence of an intercurrent event will be excluded and missing data will be assumed to be MAR.

	The secondary endpoint, number of AEs from baseline to Week 16+3 days per subject, will be reported descriptively by treatment group.
Signatory investigator	PPD , MD PPD Hannover, Germany
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

Abbreviations: AD = atopic dermatitis; AE = adverse event; EASI = Eczema Area and Severity Index; EudraCT = European Union Drug Regulating Authorities Clinical Trials Database; H4R = histamine 4 receptor; ID = identification; IMP = investigational medicinal product; IND = investigational new drug; JAK = Janus kinase; MAR = missing at random; MMRM = mixed model for repeated measurements; N = number of subjects; NCT = National Clinical Trial; PDE4i = phosphodiesterase 4 inhibitor; SFU = safety follow-up; TCI = topical calcineurin inhibitor(s); TCS = topical corticosteroid(s), vIGA-AD = Validated Investigator Global Assessment Scale for Atopic Dermatitis.

2 Trial identification

EudraCT number: 2020-004561-39.

NCT number: NCT05117060.

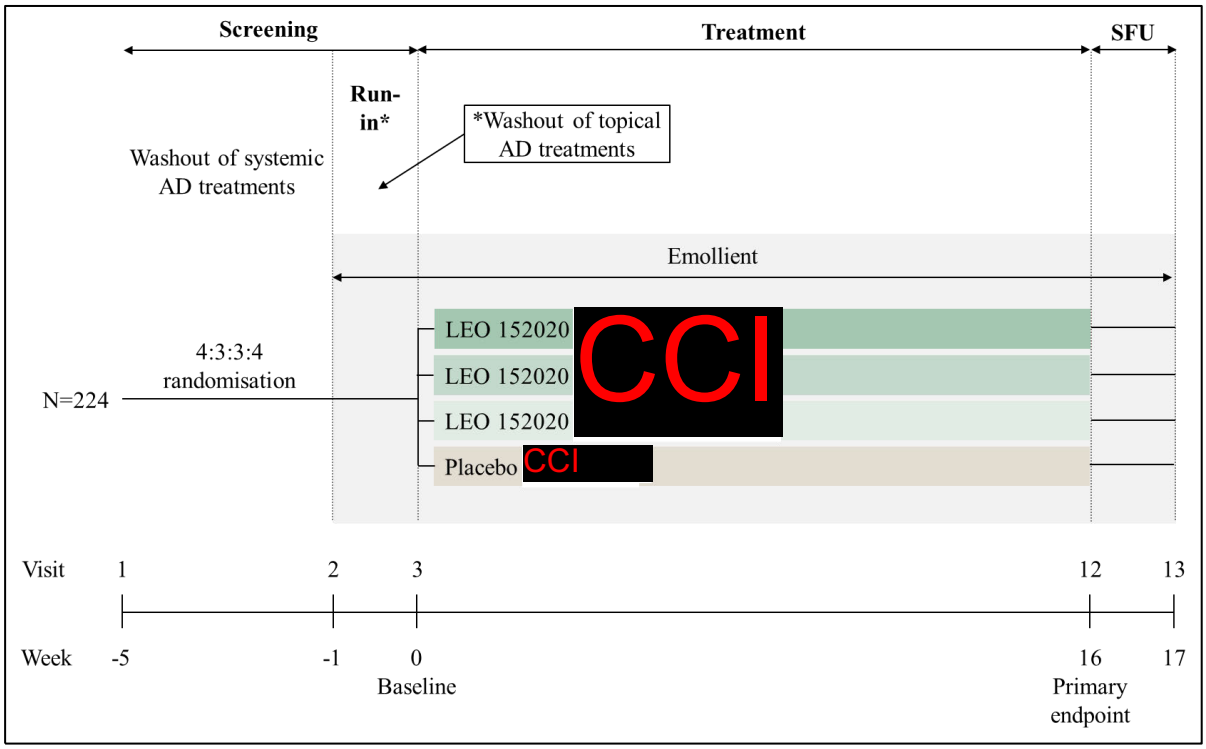
IND number: 143394.

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

3 Schematic of trial design

The trial design is illustrated in Panel 1 and described in Section 7.1.

Panel 1: Trial design



Abbreviations: AD = atopic dermatitis; N = number of subjects; SFU = safety follow-up.

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

	Screening	Screening run-in	Baseline Start of treatment	Treatment	>	>	>	>	>	>	Treatment	End of treatment [a] Primary endpoint	Safety follow up [a]	Early termination [b]	Unscheduled visit [c]	Reference
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**NA**	**NA**	
Week	**-5**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**17**	**NA**	**NA**	
Day	**-35**	**-7**	**1**	**7**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**119**	**NA**	**NA**	
Visit window (days) [d]	**NA**	**-3**	**NA**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**NA**	**NA**	
Trial population and eligibility																
Informed consent(s) [e]	X															Appendix 3B
Subject eligibility	X		X													8.1 to 8.3
Screening/baseline assessments																
Demographics	X [f]		X [f]													11.2.1
Medical history	X															11.2.3
BSA involvement [g]	X		X													11.2.4 and 11.3.3
Hepatitis B, C, and HIV	X														(X) [h]	Exclusion criteria 7 and 9
Tuberculosis test per local standard of care	X														(X) [h]	11.2.5 and Exclusion criterion 8

	Screening	Screening run-in	Baseline Start of treatment	Treatment	>	>	>	>	>	>	Treatment	End of treatment [a] Primary endpoint	Safety follow up [a]	Early termination [b]	Unscheduled visit [c]	Reference
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**NA**	**NA**	
Week	**-5**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**17**	**NA**	**NA**	
Day	**-35**	**-7**	**1**	**7**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**119**	**NA**	**NA**	
Visit window (days) [d]	**NA**	**-3**	**NA**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**NA**	**NA**	
Body measurement (height and weight)			X													11.2.2
Randomization and treatments																
Concomitant medication / concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	9.6
Background treatment (emollient)		>	>	>	>	>	>	>	>	>	>	>	>			9.4
Randomization			X													9.3.1
Dispensing of IMP			X	X	X	X	X	X	X	X	X				(X)	9.8.4
Administration of IMP at the trial site [i]			X	X	X	X	X	X	X	X	X				(X)	9.2
Treatment compliance at the trial site			X	X	X	X	X	X	X	X	X				(X)	9.8.5
Administration of IMP at the subject's home [j]			>	>	>	>	>	>	>	>	>	> [j]				9.2
Return of unused IMP				X	X	X	X	X	X	X	X	X		X	(X)	9.8.4
IMP accountability				X	X	X	X	X	X	X	X	X		X	(X)	9.8.4

	Screening	Screening run-in	Baseline Start of treatment	Treatment	>	>	>	>	>	>	Treatment	End of treatment [a] Primary endpoint	Safety follow up [a]	Early termination [b]	Unscheduled visit [c]	Reference
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**NA**	**NA**	
Week	**-5**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**17**	**NA**	**NA**	
Day	**-35**	**-7**	**1**	**7**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**119**	**NA**	**NA**	
Visit window (days) [d]	**NA**	**-3**	**NA**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**NA**	**NA**	
Subject assessments (eDiary)																
eDiary hand-out / training		X														11.5.1
eDiary completion [k]		>	>	>	>	>	>	>	>	>	>	>				11.5.1
Return of eDiary												X		X	(X)	11.5.1
Patient reported outcomes (completed at the trial site)																
POEM			X			X						X		X	(X)	11.5.7
DLQI			X			X						X		X	(X)	11.5.8
EQ-5D-5L	X		X									X		X	(X)	11.5.9
WPAI:AD			X									X		X	(X)	11.5.10
HADS			X									X		X	(X)	11.5.11
PGI-S [l]			X			X		X		X	X	X		X	(X)	11.5.12
PGI-C [m]								X		X		X		X	(X)	11.5.13
Efficacy assessments																
EASI	X	X	X	X	X	X	X	X	X	X	X	X		X	(X)	11.3.1
vIGA-AD	X	X	X	X	X	X	X	X	X	X	X	X		X	(X)	11.3.2

	Screening	Screening run-in	Baseline Start of treatment	Treatment	>	>	>	>	>	>	Treatment	End of treatment [a] Primary endpoint	Safety follow up [a]	Early termination [b]	Unscheduled visit [c]	Reference
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**NA**	**NA**	
Week	**-5**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**17**	**NA**	**NA**	
Day	**-35**	**-7**	**1**	**7**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**119**	**NA**	**NA**	
Visit window (days) [d]	**NA**	**-3**	**NA**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**NA**	**NA**	
SCORAD	X	X	X	X	X	X	X	X	X	X	X	X		X	(X)	11.3.3
Safety assessments																
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	13
Vital signs	X		X	X	X	X	X	X	X	X	X	X		X	(X)	11.4.1
Physical examination	X		X			X		X		X		X		X	(X)	11.4.2
ECG	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	(X)	11.4.3
Urine dipstick (urinalysis) [o]	X		X			X		X		X		X	X	X	(X)	11.4.4
Clinical chemistry, hematology	X	X	X			X		X		X		X	X	X	(X)	11.4.4
Urine pregnancy test [p]			X			X		X		X			X	X	(X)	11.4.4
Serum pregnancy test [p]	X											X		X	(X)	11.4.4
Pharmacokinetic and pharmacodynamic assessments																
PK blood sample(s)			X [n]	X [n]		X [n]		X [n]		X [n]		X [n]		X [n]	(X)	11.6.1
PD blood biomarkers			X			X		X				X		X	(X)	11.6.2

	Screening	Screening run-in	Baseline Start of treatment	Treatment	>	>	>	>	>	>	Treatment	End of treatment [a] Primary endpoint	Safety follow up [a]	Early termination [b]	Unscheduled visit [c]	Reference
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**NA**	**NA**	
Week	**-5**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**17**	**NA**	**NA**	
Day	**-35**	**-7**	**1**	**7**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**119**	**NA**	**NA**	
Visit window (days) [d]	**NA**	**-3**	**NA**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**NA**	**NA**	
Optional assessments [q]																
Wristband actigraphy		>	>	>	>	>	>	>	>	>	>	>				11.7.2
Return of the wristband actigraphy devices [r]			X	X	X	X	X	X	X	X	X	X		X	(X)	11.7.2
Skin biopsies (skin biomarkers) [s]			X									X		X	(X)	11.7.3
Check of wound healing				X									X	(X)	(X)	11.7.3
Exit interview [t]												X				11.7.4
End of treatment/trial																
End of treatment form												X		X		11.8
End of trial form													X	X		11.8

Abbreviations: AD = atopic dermatitis; ADSD = atopic dermatitis symptom diary; AE = adverse event; BSA = body surface area; CTP = clinical trial protocol; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eCRF = electronic case report form; eDiary = electronic diary; EQ-5D-5L = EuroQoL (Quality of Life) 5-Dimension Health Questionnaire 5 Level; HADS = Hospital Anxiety and Depression Scale; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; IFN = interferon; IMP = investigational medicinal product; NA = not applicable; PD = pharmacodynamic(s), PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic(s); POEM = Patient-oriented Eczema Measure; PRO = patient reported outcome; SCORAD = Scoring Atopic Dermatitis; vIGA-AD = Validated Investigator Global

Assessment Scale for Atopic Dermatitis; CCI ; WPAI:AD = Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis; (X) = assessment/procedure to be conducted, if applicable.

[a] An end-of-treatment form and end-of-trial form must be completed in the eCRF for all randomized subjects.

[b] Subjects who permanently discontinue IMP prior to Week 16 and subjects who withdraw from the trial will be asked to come to an early termination visit. Discontinued/withdrawn subjects should be followed up as described in Section 10.3.

[c] If necessary, (an) unscheduled visit(s) may be added to the subject's schedule, e.g. due to an AE, a significant change in disease state, or difficulty complying with the CTP requirements. At an unscheduled visit, the investigator should at least collect AE data. Other assessments/procedures to be conducted will be at the discretion of the investigator.

[d] If the date of a visit does not conform to the schedule of trial procedures, subsequent visits should be planned to maintain the visit schedule relative to baseline/randomization.

[e] The informed consent form must be signed prior to conducting any protocol-related assessments/procedures, including but not limited to screening evaluations and washout of disallowed medications. Screening evaluations may start later than the date when the informed consent form was signed.

[f] At screening, the demographic data listed in Section 11.2.1 will be recorded. At baseline, only age will be recorded on the randomization form.

[g] BSA affected by AD will be assessed as component A of SCORAD (Section 11.3.3).

[h] If the results of the hepatitis B, C, HIV, and/or tuberculosis tests are inconclusive at screening, they may be repeated at an unscheduled visit, if necessary.

[i] At each visit between baseline and Week 14, the subject will self-administer the morning dose of IMP at the trial site under the supervision of the site staff.

[j] Between visits from baseline to Week 16, the subject will self-administer the IMP at their home. The subject will take their last dose of IMP in the evening before the Week 16 visit.

[k] ADSD, Nocturnal CCI Difficulty CCI Frequency of CCI During the Night, CCI and CCI will be completed in the eDiary daily.

[l] Includes ADSD PGI-S, CCI PGI-S, Nocturnal CCI PGI-S, Difficulty CCI PGI-S, Frequency of CCI During the Night PGI-S, CCI PGI-S, and CCI PGI-S.

[m] Includes ADSD PGI-C, CCI PGI-C, Nocturnal CCI PGI-C, Difficulty CCI PGI-C, Frequency of CCI During the Night PGI-C, CCI PGI-C, and CCI PGI-C.

[n] See Panel 3 for more information.

[o] It will be at the discretion of the investigator if a urine sample should be sent to the central laboratory for further analysis.

[p] Women of childbearing potential only.

[q] Wristband actigraphy, skin biopsies, and exit interviews are optional components of the trial for subgroups of subjects. Participation in these components is not required for participation in the core part of the trial and the subject will be asked to provide additional consent.
[r] At the indicated visits, subjects will be asked to bring the wristband actigraphy devices back to the site and the investigator or site staff will transfer data from the devices. Subjects will be asked to return the devices at Week 16 or at their last visit in the trial.
[s] Skin biopsies should be taken from the locations described in Section 11.7.3.
[t] Exit interviews should be scheduled as described in Section 11.7.4.

Panel 3: Schedule of ECG measurements and PK blood samples in relation to fasting and administration of IMP

Week -5 (screening)	Week -1 (run-in)	Week 0 (baseline)	Week 1	Weeks 2, 6, 10, and 14	Weeks 4, 8, and 12	Week 16	Week 17 (safety follow-up)	Early termination
NA	NA	**Subject is fasted [c]**					NA	NA
• 3 consecutive ECGs [a] • Laboratory assessments	• 1 ECG [b] • Laboratory assessments	• Pre-dose ECG [d] • Pre-dose PK [e] • Laboratory assessments			• Pre-dose PK [g] • Laboratory assessments	• 1 ECG [b] • 1 PK • Laboratory assessments	• 1 ECG [b] • Laboratory assessments	• 1 ECG [b] • 1 PK • Laboratory assessments
NA	NA	**Administration of IMP** **Wait [CCI] and proceed with**				**Subject may break fast**	NA	NA
		• Post-dose ECG • Post-dose PK [f]	• Post-dose ECG • Post-dose PK [f]	• Post-dose ECG	• Post-dose ECG • Post-dose PK [f]			
NA	NA	**Subject may break fast**				NA	NA	NA
		• Japan: post-dose ECG (4 hours±15 min after dosing) [h]	• Japan: post-dose ECG (4 hours±15 min after dosing) [h]					

Abbreviations: ECG = electrocardiogram; IMP = investigational medicinal product; NA = not applicable, PK = pharmacokinetic(s).
If at any ECG measurement, the subject presents with a [CCI], the ECG should be repeated. If the [CCI] is confirmed, a PK sample (if not already planned at the visit) must be taken close to the last ECG. See Section 11.4.3 for more information.

[a] In line with exclusion criterion 13. Must be measured before any blood sample collected at the same visit.
[b] Must be measured before any blood sample collected at the same visit.
[c] The subject will be asked to come fasted to the trial site, i.e. arrive at the site minimum 2 hours after their last meal.
[d] Must be measured before any blood sample collected at the same visit and shortly before IMP administration.
[e] Should be taken within 5-10 min of the pre-dose ECG measurement shortly before IMP administration.
[f] Should be taken within 5-10 min of the post-dose ECG measurement, i.e. CCI after dosing.
[g] Should be taken shortly before IMP administration.
[h] See also Appendix 4.

5 Introduction and trial rationale

5.1 Atopic dermatitis

AD is a chronic inflammatory skin disease, often referred to as eczema and characterized by widespread skin lesions, manifested as red, itchy, swollen, cracked, weeping lesions with crusting/scaling, intractable itch (pruritus), and enhanced susceptibility to bacterial and viral skin infections. Persistent itch that often causes sleep deprivation and disfiguration of the skin substantially impairs patients' quality of life (1, 2). In a subset of patients, onset of AD precedes that of other conditions such as food allergies, asthma, and allergic rhinitis in a pattern known as the atopic march (3). AD has a worldwide lifetime prevalence of 15 to 20% in children (4) and up to 10% in adults (5, 6) and its prevalence has increased 2- to 3-fold during the past 3 decades in industrialized countries (5). Pathophysiology of AD is complicated and regulated by several genetic and environmental factors. However, it is believed to be mainly driven by Th2 cell responses (7, 8).

Itch can be defined as an unpleasant cutaneous sensation associated with the immediate desire to scratch and has been attributed to increased release of various itch mediators such as histamine. Itch is known to be a common symptom in dermatologic and systemic diseases (9). Although numerous substances such as substance P, serotonin, IL-31, and tryptase are known to cause itch, histamine is also well known to evoke itch when applied to the skin (10, 11).

Itch is a primary symptom of AD and can occur both during the day and at night. Nocturnal itch can significantly impact a patient's sleep and quality of life (12, 13). Nocturnal scratching can lead to difficulties falling asleep and frequent awakening (14). The resulting fatigue and difficulty concentrating can prevent the patient from fully engaging in school, work, hobbies, and socially (15). In addition, persistent scratching can lead to secondary impacts of AD such as decreased skin barrier function and increased risk of infection, as well as disfigurement, scarring, and other complications (16, 17).

Treatment recommendations for AD include topical treatments, mainly TCS. However, not all patients with moderate to severe AD are adequately treated with TCS and TCI. TCS and oral systemic treatments (e.g. cyclosporine, azathioprine) are all associated with toxicities when used in the long-term (18-20). Therefore, patients with moderate to severe AD experience a high unmet need for alternative AD treatments.

Since histamine levels are highly elevated in inflamed skin (21), it is possible that histamine is involved in inflammatory skin pathology. However, antagonists blocking H1R or H2Rs are largely ineffective in reducing chronic symptoms of AD (22, 23). H4R was discovered in the early 2000s and various selective H4R antagonists have allowed understanding the expression and function of the H4 receptor (24, 25). Research on H4R has shown that H4R antagonists have anti-pruritic and anti-inflammatory effects in inflammatory mouse models (26, 27) and in clinical trials in AD (28, 29). Therefore, H4R may present a novel therapeutic target in AD.

5.2 Experience with investigational medicinal product

An overview of nonclinical and clinical data on LEO 152020 is available in the current edition of the investigator's brochure (30).

5.2.1 Nonclinical data

LEO 152020 binds selectively to human H4R and has been characterized as antagonist, inhibiting the histamine-induced effects of the H4R. CCI [redacted]

In safety pharmacological studies, LEO 152020 did not have any neurobehavioral and respiratory effects. Oral dosing in monkeys at dose levels up to CCI mg/kg did not result in any changes in body temperature, blood pressure, or heart rate, and there were no clinical signs of AChE inhibition. ECG monitoring showed a CCI [redacted] at doses CCI mg/kg with no biological significance in the monkey.

Ex vivo and in vivo models have shown that LEO 152020 has CCI [redacted] efficacy and in addition has CCI [redacted] in several models of pruritus in mice.

In a 26-week rat toxicology study, histopathological investigation showed an CCI [redacted] CCI [redacted] in the CCI [redacted] compared with their control. CCI [redacted] were also observed and considered secondary to the findings in the CCI [redacted] These findings were observed at the highest dose level tested (CCI [redacted]) and were partially reversed after a CCI [redacted] recovery period. In this study, NOAEL was CCI [redacted] mg/kg/day for CCI [redacted] corresponding to a safety margin of CCI [redacted] and an exposure margin of CCI [redacted] to the therapeutic dose of LEO 152020 CCI [redacted]

The pharmacokinetic profile of LEO 152020 was investigated in mice, rats, and monkeys. The main route of elimination was urinary and the unchanged parent compound was the

predominant component in all urine, feces, and plasma. No metabolites observed were >5% of the dose administered. LEO 152020 was evaluated to be non-genotoxic and with no phototoxic potential. Repeated-dose studies in rats and monkeys up to 16 weeks revealed a toxicity profile amenable to clinical monitoring and of low concern for human risk and provided adequate safety margins.

5.2.2 Clinical data

A first-in-human clinical trial (JWP-FRC-101) in healthy Korean, Caucasian, and Japanese subjects (88 subjects) was completed. This trial contained single-ascending dose (CCI mg) and multiple ascending dose (CCI mg) parts. There were emerging CCI tolerability issues observed in the CCI cohort (highest dose tested), CCI cohort and CCI cohort. All of these CCI events were classified as mild, occurred rapidly after dosing, and the majority of events resolved within 1-3 hours. In addition, 1 SAE was observed for the lowest single dose (CCI mg) and considered not related to LEO 152020 by the sponsor. There were no other SAEs reported in the other dose groups.

Given the mild severity, fast onset, and transient nature of the CCI events, and that the events were primarily observed at the higher dose levels in the first-in-human trial, these events were not considered a safety concern and are not expected to be relevant at the therapeutic doses given in this trial.

Single dose administration of LEO 152020 resulted in an CCI with the mean and upper bound of the 90% CI of CCI exceeding CCI at single doses of CCI and CCI mg (31). CCI effect was observed in the CCI and CCI mg multiple dose groups where the upper bound of the 90% CI exceeded CCI (CCI, respectively). The mean effect in the CCI and CCI mg multiple dose groups were CCI and CCI, respectively. Furthermore, in the multiple dose but not the single dose part of the trial, a dose dependent CCI was observed with a CCI of CCI in the CCI mg dose group. In the CCI dose group, the CCI was CCI Thus, it is unlikely that these findings are clinically relevant at the therapeutic doses given in this trial.

5.3 Trial rationale

This trial will provide information on the efficacy and safety of LEO 152020 and on the exposure-response relationship of LEO 152020. This will allow identification of efficacious dose(s) of LEO 152020 to inform further clinical development.

The trial design is presented in Section 7.1 and illustrated in Section 3. The scientific rationale for the trial design is presented in Section 12.

5.4 Ethical considerations

This trial will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki (32) and ICH GCP (33) and in compliance with the approved protocol and applicable regulatory requirements.

The trial design is considered scientifically justified and to adhere to ethical standards ensuring the rights, safety, and well-being of the subject. The efficacy and safety of LEO 152020 will be evaluated in adults with moderate to severe AD who may benefit from treatment with LEO 152020. Appropriate measures will be taken to protect the subject from potential risks related to treatment with LEO 152020 and to closely monitor the subject (Section 5.5).

Participation in the trial is voluntary and the subject may discontinue IMP and/or withdraw from the trial at any time. If a subject is withdrawn from the trial, they will be treated at the discretion of the investigator or referred to (an)other physician(s) according to standard practice.

Women who are pregnant (or trying to become pregnant) and women who are breastfeeding will be excluded from participation in the trial. Women of childbearing potential must agree to use highly effective contraception to prevent pregnancy during the trial. In addition, pregnancy tests (urine and serum) for all women of childbearing potential will frequently be conducted during the trial to detect any pregnancies.

Subjects not able to provide informed consent will be excluded from participation in the trial.

It will be explained to the subject that the trial will consist of core assessments/procedures and optional components not required for participation in the core part of the trial and for which the subject will be asked to provide additional consent.

In accordance with the current version of ICH and GCP guidelines, qualified medical personnel employed by LEO Pharma will be readily available to advise on trial-related medical questions. Medical monitoring will be conducted throughout the trial to ensure subject safety during their participation in the trial. Safety data will be reviewed by qualified personnel to ensure that prompt action is taken, if needed, to protect the subject.

5.5 Benefit/risk assessment

There is a clear, unmet need for safe, long-term treatment options for subjects with moderate to severe AD and treatments adequately addressing itch. As a novel oral H4R antagonist, LEO 152020 is expected to be efficacious against both inflammation and itch caused by AD. Oral treatment is often considered a more convenient route of administration for the patient and one resulting in higher compliance than topical or subcutaneous treatments.

The subject will be informed of the possibility and probability of receiving active or placebo treatment. In this trial, approximately 71% of the subjects will receive active treatment with LEO 152020 in dose regimens believed to have a therapeutic effect on AD (Section 12.1) and 29% of the subjects will receive placebo (Section 9.3.1).

All subjects will be followed-up closely by a physician during their treatment and will be able to monitor their own disease via the use of an electronic Diary (Section 11.5.1). Subjects will also be offered to participate in an optional component of the trial involving the study of nocturnal CCI and sleep CCI (Section 11.7.2).

Risks to subjects will be minimized by inclusion of subjects fulfilling all eligibility criteria (Sections 8.1 to 8.3). In addition, close clinical monitoring (Section 4) and discontinuation/withdrawal criteria will ensure subject safety during the trial (Section 10.2). In addition to appropriate safety monitoring, an independent DMC will be established which will review safety data and assess overall trial conduct periodically as well as issue recommendations to LEO Pharma as to the pursuit of the trial (Appendix 3H).

The subject will be informed that changes to their ongoing AD treatment may be required during the screening period and that their condition may as a result worsen. Therefore, investigators will be asked only to include subjects who are considered able to discontinue prohibited medications without experiencing intolerable worsening of AD.

If medically necessary (i.e. to control intolerable worsening of AD symptoms), rescue treatment of AD may be provided to the subject at the discretion of the investigator (Section 9.5).

Blood sampling presents the usual low risk normally associated with this procedure and will only be conducted by qualified medical personnel.

Nocturnal CCI and sleep CCI monitoring by wristband actigraphy is not considered to bear a risk (Section 11.7.2). A hypoallergenic bandage can be placed under each of the wristband actigraphy devices to prevent skin irritation on the wrists.

Risks for subjects treated with LEO 152020

Due to the important potential risk of CCI, the dose regimens explored in this trial have been chosen to minimize that risk for the subjects. The highest dose regimen in the trial (CCI is predicted to result in concentration levels below those of the CCI mg once daily dose regimen, which in the first-in-human trial resulted in a mean CCI of CCI with an upper bound of the 90% CI for CCI (CCI) at CCI (Section 5.2.2). Since subjects with mild and moderate renal impairment may exhibit increased exposure of LEO 152020, ECGs will be measured at each visit (Section 4) to monitor the individual subjects in line with CCI for drugs for which a CCI cannot be excluded (Panel 2).

To further ensure subject safety, subjects with cardiac arrhythmic risk factors, moderate and severe hepatic impairment, and/or severe renal impairment will be excluded from participation in the trial (Section 8.3). Subjects using medications for which CCI is a known side effect and which cannot be replaced by safe alternative medication(s) will be excluded from participation in the trial (Section 9.7). Moreover, medications known to inhibit the CCI CCI, and/or CCI will be prohibited during the trial (Section 9.7 and Appendix 8). Frequent ECG monitoring will be conducted with pre- and/or post-dose ECGs measured and evaluated at the sites and centrally (Section 11.4.3). At selected visits, ECG and PK blood samples collected at the same timepoint will be used to explore the relation between exposure of LEO 152020 and potential CCI (Section 4). In the multiple dose part of the first-in-human trial, a dose-dependent CCI in heart rate was observed with a CCI CCI (CCI) in the CCI dose group. If a subject develops CCI and CCI, the risk of CCI may increase. To mitigate this, ECGs will be taken at each visit (Section 4) to monitor all subjects.

In the first-in-human clinical trial, mild CCI adverse events were observed following treatment with high doses of LEO 152020. As CCI may increase the risk of CCI, additional monitoring of CCI should be arranged, at the discretion of the investigator, for subjects who experience prolonged episodes of CCI during the treatment period.

Risks for subjects who consent to provide skin biopsies
Subjects who consent to provide skin biopsies may experience discomfort associated with the collection of the samples. To alleviate this, the subject will receive an injection of a local anesthetic to numb the area where the biopsy will be taken. Complications of skin biopsies may include bleeding, bruising and/or pain, and infection at the biopsy site. Pressure dressings and ice can be used to help alleviate these symptoms. Wound healing at the biopsy site will be checked at a subsequent visit. The subject will be informed that they may retain small scars after the procedure.

Risks associated with the COVID-19 pandemic
Participation in clinical trials may currently be associated with increased risks and challenges due to the COVID-19 pandemic caused by SARS-CoV-2. EMA (35), FDA, and national health authorities across the world have issued guidelines aiming at providing recommendations for conducting clinical trials during the COVID-19 pandemic. Subjects and sites are expected to follow the recommendations and preventive measures issued by their local health authorities.

LEO Pharma has evaluated currently available safety data on LEO 152020. Based on nonclinical studies, LEO 152020 is considered a mild immunomodulatory compound and its mechanism of action is not believed to present a risk of decreased anti-viral immunity in subjects infected by COVID-19. In addition, LEO 152020 is not believed to increase the susceptibility of the subject to contract COVID-19 or other infections.

However, adhering to the schedule of trial procedures in the context of a pandemic, entails a risk of increased exposure to SARS-CoV-2 by spending time in public areas (e.g. commuting to and from the trial site, dwelling at the hospital for the time of the visit) and having increased human contacts (e.g. with the site staff). Given the rapidly evolving epidemic situation and the potential for the pandemic to relapse, LEO Pharma will carefully monitor the pandemic situation and issue risk mitigation measures to protect subjects and staff involved in the trial while ensuring integrity of the trial data. A COVID-19 contingency plan is presented in Appendix 9.

With the above provisions in place, the risks associated with participating in the trial are considered low and outweighed by the benefit of a potential future oral treatment option for AD. Therefore, the currently expected benefit/risk profile is considered in favor of conducting the trial.

6 Trial objectives, estimands, and endpoints

Trial objectives and endpoints are presented in Panel 4. An estimand framework is used for the primary endpoint to ensure that occurrence of intercurrent events is taken into account. Further details about the estimands and statistical analyses of the endpoints are presented in Section 14.3.

Panel 4: Objectives and endpoints

Objectives	Endpoints
Primary objective (continues)	
To explore the exposure-response relationship of LEO 152020 and evaluate efficacy of LEO 152020 compared with placebo for up to 16 weeks of treatment in subjects with moderate to severe AD (continues)	Primary endpoint • Change in EASI from baseline to Week 16. Exploratory endpoints • EASI at each visit from Week 1 to Week 16. • Having a decrease in EASI of at least 50% (EASI 50) from baseline to Week 16. • Time from randomization to having an observed decrease in EASI of at least 50% (EASI 50) from baseline. • Having a decrease in EASI of at least 75% (EASI 75) from baseline to Week 16. • Having a decrease in EASI of at least 90% (EASI 90) from baseline to Week 16. • Having vIGA-AD of 0 (clear) or 1 (almost clear) at Week 16. • Having a decrease in vIGA-AD of at least 2 points from baseline to Week 16. • SCORAD at each visit from Week 1 to Week 16. • Change in ADSD score (weekly average) from baseline to Week 16. • Change in each ADSD individual symptom score [a] (weekly average) from baseline to Week 16. • Having a decrease in ADSD CCI score (weekly average) of at least 4 points from baseline to Week 16 in subjects with ADSD CCI score ≥4 at baseline.

Objectives	Endpoints
Primary objective (continued)	
To explore the exposure-response relationship of LEO 152020 and evaluate efficacy of LEO 152020 compared with placebo for up to 16 weeks of treatment in subjects with moderate to severe AD (continued)	• Time from randomization to having a decrease in ADSD CCI score (weekly average) of at least 4 points from baseline in subjects with ADSD CCI score ≥4 at baseline.
Secondary objectives	
To evaluate the safety of LEO 152020 compared with placebo in subjects with moderate to severe AD	Secondary endpoints • Number of AEs [b] from baseline to Week 16+3 days per subject.
Exploratory objectives (continues)	
To evaluate effect of treatment with LEO 152020 compared with placebo for up to 16 weeks of treatment on PROs in subjects with moderate to severe AD	Exploratory endpoints • Change in POEM from baseline to Week 16. • Change in DLQI from baseline to Week 16. • Having a decrease in DLQI of at least 4 points from baseline to Week 16 in subjects with DLQI ≥4 at baseline. • Change in EQ-5D-5L from baseline to Week 16. • Change in HADS from baseline to Week 16. • Change in WPAI:AD (for each individual domain) from baseline to Week 16. • Having a decrease in POEM of at least 4 points from baseline to Week 16 in subjects with POEM ≥4 at baseline.
Exploratory objectives (continued)	
To evaluate pharmacokinetic parameters of LEO 152020 for up to 16 weeks of treatment in subjects with moderate to severe AD	Exploratory endpoint • C_{trough} of LEO 152020 at Weeks CCI [redacted]. • C_{max} of LEO 152020 at Weeks CCI [redacted].

Objectives	Endpoints
To evaluate effect of treatment with LEO 152020 compared with placebo for CCI of treatment on disease biomarkers and biomarkers related to the mechanism of action of LEO 152020 in subjects with moderate to severe AD	Exploratory endpoints • Change in expression levels of blood biomarkers from baseline to CCI • Change in expression levels of AD disease biomarkers in skin from baseline to CCI
To explore the effect of treatment with LEO 152020 compared with placebo for CCI of treatment on sleep disturbance and nocturnal CCI in subjects with moderate to severe AD	Exploratory endpoints Based on eDiary data • Difficulty CCI at Week CCI • Frequency of CCI During the Night at Week CCI • CCI at Week CCI • CCI at Week CCI Based on actigraphy data • Change in CCI from baseline to Week CCI • Change in CCI from baseline to Week CCI • Change in number of nocturnal CCI events per hour from baseline to Week CCI • Change in duration of nocturnal CCI per hour from baseline to Week CCI

Abbreviations: AD = atopic dermatitis; ADSD = Atopic Dermatitis Symptom Diary; AE = adverse event; C_{max} = maximum serum concentration; C_{trough} = lowest IMP concentration before the next dose of IMP is administered; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI 50 = decrease in EASI of at least 50% from baseline; EASI 75 = decrease in EASI of at least 75% from baseline; EASI 90 = decrease in EASI of at least 90% from baseline; ECG = electrocardiogram; EQ-5D-5L = EuroQoL 5-Dimension Health Questionnaire 5 Level; HADS = Hospital Anxiety and Depression Scale; IMP = investigational medicinal product; POEM = Patient-oriented Eczema Measure; PRO = patient-reported outcome; CCI ; CCI ; CCI ; SCORAD = Scoring Atopic Dermatitis; vIGA-AD = Validated Investigator Global Assessment Scale for Atopic Dermatitis; CCI ; WPAI:AD = Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis.

[a] Includes CCI

[b] Treatment emergent AEs (Section 14.3.14.1).

7 Trial design

7.1 Overall trial design

Overview
This is a phase 2 randomized, triple-blind, placebo-controlled, parallel-group, international trial to evaluate the efficacy and safety of orally-administered LEO 152020 tablets (CCI CCI and CCI compared with placebo tablets for up to 16 weeks of treatment in adults with moderate to severe AD.

The trial will consist of:

- A screening period of maximum 5 weeks (at the earliest Week -5 to baseline) including a run-in period of 1 week (Week -1 to baseline).
- A treatment period of 16 weeks (baseline to Week 16).
- A safety follow-up period of 7 days (Week 16 to Week 17).

Randomization will take place at baseline. The primary endpoint will be assessed at Week 16. The final safety assessments will be conducted at Week 17.

The subject's visit schedule and the assessments/procedures to be conducted at each visit are presented in Section 4. The trial rationale is presented in Section 5.3 and the scientific rationales for trial design are presented in Section 12.1.

Screening period
In the screening period, eligibility of the subject to participate in the trial will be evaluated. From the screening visit, the subject will be asked to stop any systemic AD treatment (Section 8.3 and Section 9.7).

The screening period will include a run-in period (Week -1 to baseline). From the run-in visit (Week -1), the subject will be asked to stop any topical AD treatment with TCS, TCI, PDE4i, and/or topical JAK inhibitors and to apply an emollient (background treatment, Section 9.4). The subject will be asked to apply the emollient at least twice daily and for at least 7 days prior to the planned randomization (baseline).

At the run-in visit, the subject will receive an eDiary and training in using the device. From Week -1, the subject will be asked to complete the eDiary for 7 days prior to randomization (Section 11.5.1).

At the run-in visit, subjects who consented to participate in wristband actigraphy will receive 2 actigraphy devices. From Week -1, the subjects will be asked record scratch and sleep data with the devices daily (Section 11.7).

The total duration of the screening period including the run-in period will depend on the time needed for washout of the systemic AD treatment(s) by baseline and may last for a maximum of 5 weeks, as applicable. It will be recorded in the eCRF if washout was required and which treatment(s) were stopped.

Re-screening of subjects is not allowed unless the screening failure was due to an administrative reason (Section 8.4).

Randomization
At baseline, the subject will be randomized to 1 of 4 oral treatments as described in Section 9.3.1.

Treatment period
In the treatment period, the subject will be asked to self-administer LEO 152020 or placebo tablets twice daily for 16 weeks (Section 9.2). In this period, the subject will be asked to continue applying the emollient as needed and complete the eDiary. If the subject has provided additional consent, optional assessments and procedures may apply (see Section 11.7). The subject will also be asked to visit the site for assessments and procedures.

Safety follow-up period
In the safety follow-up period, the subject will be asked to stop treatment with LEO 152020 or placebo tablets and the safety of the treatment will further be assessed at the safety follow-up visit (Week 17). In this period, the subject may continue applying the emollient as needed. Continued treatment of the subject's AD should at the earliest resume after the safety follow-up visit (or the last visit of the subject in the trial for discontinued/withdrawn subjects).

7.2 Number of subjects needed

224 subjects (including 28 Japanese subjects) are planned to be randomized in the trial.

Based on an anticipated screening failure rate of 30-35%, between 292 and 304 subjects should be screened for the trial.

The trial will be conducted at approximately 60 sites in Europe, North America, Japan, and Australia.

The statistical power considerations for this sample size are described in Section 14.1.

7.3 End-of-trial definition

A subject will be considered to have completed the trial if they have completed all trial periods including the safety follow-up visit at Week 17 (see Section 11.8 for data to be recorded on the end-of-trial form).

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

Final data collection for evaluation of the primary endpoint will occur at Week 16. Therefore, the primary completion date is defined as the date of last Week 16 visit for the last subject in the trial globally.

Data monitoring committee
An independent DMC will assess subject safety and overall trial conduct periodically (Appendix 3H). Based on their assessment, the DMC will issue recommendations to LEO Pharma as to the pursuit of the trial. Depending on the DMC's recommendations, LEO Pharma may decide to terminate the trial prematurely in interest of subject safety. Organization and operation of the DMC will be described in a separate DMC charter. Data to be provided to the DMC for their assessment will be described in a separate DMC statistical plan.

8 Trial population

8.1 Subject eligibility

The investigator should only include subjects who meet all eligibility criteria, are not put at undue risk by participating in the trial, and can be expected to comply with the protocol.

The subject's eligibility for the clinical trial must be verified according to the inclusion and exclusion criteria according to the schedule of trial procedures (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

The subjects must fulfil all of the following criteria to be eligible for the trial:

1. Signed and dated informed consent obtained prior to any protocol-related procedures.
2. Adult, age 18 years or older at screening.
3. Diagnosis of chronic AD as defined by the Hanifin and Rajka (1980) criteria for AD (36).
4. History of AD ≥1 year prior to baseline.
5. Recent (within 6 months prior to baseline) documented history of inadequate response to topical AD treatments* or subject for whom topical AD treatments are medically inadvisable.

   *Inadequate response to topical AD treatments is defined as failure to achieve and maintain remission or a low disease activity state corresponding to 0 (clear) ≤ IGA ≤ 2 (mild) despite treatment with a daily regimen of TCS of medium to high potency (±TCI, as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g. 14 days for super-potent TCS).
6. 7.1≤ EASI ≤50 at baseline.

7. vIGA-AD score ≥3 at baseline.

8. BSA ≥5% at baseline.

9. Subject agrees to apply an emollient to lesional and non-lesional skin at least twice daily for at least 7 consecutive days immediately prior to baseline.

10. Women of childbearing potential* must use highly effective contraception** from randomization to the end of the trial (safety follow-up visit).

    * A woman of childbearing potential is defined as a female subject aged ≥12 years or a younger girl who, at the discretion of the investigator, is deemed to be of reproductive potential. A woman is defined as not being of childbearing potential if she is postmenopausal (at least 12 months with no menses without an alternative medical reason prior to screening), or surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

    **A highly effective method of contraception is defined as one which results in a low failure rate (less than 1% per year when used correctly and consistently) such as:

    - Bilateral tubal occlusion.
    - IUD.
    - IUS.
    - Combined (estrogen- 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 lifestyle of the subject and not just being without a current partner).
    - Same-sex partner.
    - Vasectomized partner (given that the subject is monogamous).

8.3 Exclusion criteria

Subjects are not eligible for the trial if they violate any of the following criteria:

1. Concurrent skin disease at baseline which may interfere with the trial assessments, at the discretion of the investigator.

2. Active skin infection or any other clinically apparent infection at baseline which may interfere with the trial assessments, at the discretion of the investigator.

3. Previous treatment with an oral H4R antagonist (including LEO 152020) within 6 months prior to baseline.

4. Previous treatment with 3 or more systemic AD treatments prior to screening.

5. Systemic treatment including systemic corticosteroids known or suspected to have an effect on AD within 4 weeks or 5 half-lives prior to baseline, whichever is longer.

6. Phototherapy within 4 weeks prior to baseline.

7. Positive HBsAg, anti-HBs*, anti-HBc, or HCV serology at screening.

   *Subjects with positive anti-HBs are eligible provided that they have a negative HBsAg, negative anti-HBc (blood pattern in vaccinated subjects), and negative HCV serology.

8. Current active tuberculosis based on test per local standard at screening. The screening for tuberculosis should be done according to guidelines for patients subject to biologic treatment as per local standard of care.

9. Infection with HIV.

10. History of lymphoproliferative disease or malignancy (except treated and recovered non-melanoma skin cancer or cervical carcinoma in situ) within 5 years prior to screening.

11. Subjects at risk for Torsade de Pointes based on any of the following:

    a. Uncorrected hypokalemia or hypomagnesemia at Week -1, history of cardiac failure, history of clinically significant/symptomatic bradycardia.

    b. CCI [redacted] or family history of idiopathic sudden death.

12. Use within 5 half-lives prior to screening of concomitant medication for which CCI [redacted] is a known side effect and which cannot be discontinued or replaced by (a) safe alternative medication(s).

13. Resting QTcF (average of a triplicate measurement) <300 ms or >450 ms (men) or >460 ms (women) at screening.

14. Known history of ventricular arrhythmias.

15. Second- or third degree- atrioventricular block.

16. Subjects with severe renal impairment as determined by eGFR levels below 30 mL/min at screening (37). For eGFR levels allowed in Germany and Japan, see Appendix 4.

17. Subjects with medical history of chronic moderate to severe liver disease.

18. Clinically significant abnormal finding* at screening and/or baseline which, in the opinion of the investigator, may:

    a. Affect subject safety and well-being or put the subject at risk because of their participation in the trial.

    b. Influence the assessments.

    c. Impede the subject's ability to complete the trial.

    *Examples include clinically significant abnormal vital sign, physical examination, ECG (based on central ECG report), and laboratory result.

19. Any unstable medical, surgical, psychiatric, or additional physical disorder* at any time during the trial which, in the opinion of the investigator, may:

    a. Affect subject safety and well-being or put the subject at risk because of their participation in the trial.

    b. Impede the subject's ability to complete the trial.

    *Examples include but are not limited to endocrine, gastrointestinal, hepatic, immunological, infectious, metabolic, musculoskeletal, neurological, and major physical impairment.

20. Known or suspected hypersensitivity to any components of the IMPs or to drugs of a similar chemical class.

21. Treatment with any nonmarketed drug substance (that is, an agent which has not yet been made available for clinical use following registration) within 4 weeks or 5 half-lives of the drug prior to baseline, whichever is longer.

22. Current participation in any other interventional clinical trial.

23. Previously screened* in this trial.

    *Re-screening of subjects is not allowed unless the screening failure was due to an administrative reason (Section 8.4).

24. Current or recent chronic alcohol or drug abuse within 12 months prior to screening.

25. Subjects, who, in the opinion of the investigator, would be noncompliant or unable to understand the trial and give adequately informed consent.

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

27. Subjects who are legally institutionalized.

28. Women who are pregnant, intend to become pregnant, or are lactating.

8.4 Screening and screening failures

Subject identification number
Trial participation begins once written informed consent is obtained (Appendix 3B). Once informed consent is obtained, a subject ID will be assigned to the subject by a central IRT system.

After a subject ID has been assigned, the screening evaluations to assess eligibility may begin. The date of first screening activity can be the same as when informed consent was obtained or a later date. The subject ID will be used to identify the subject during screening and throughout the trial, if applicable. Subjects who have given written informed consent to participate in the trial and who have been assigned a subject ID are considered 'screened' subjects.

Investigator logs
The investigator will maintain a log of all subjects considered for screening, whether they provided written informed consent or not (screening log). This log will be anonymous and will include the allocated subject ID and the reason(s) for not entering the trial, if applicable. In addition, the investigator will maintain a log of all consented subjects (subject identification log). 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.

Screening failures
Screening failures are defined as subjects who consent to participate in the trial but who are subsequently not randomized to treatment. A minimal set of screening failure information is required to ensure transparent reporting of screening failures to meet the CONSORT publishing requirements (38) and to respond to queries from regulatory authorities. As a minimum, the following data will be recorded in the eCRF for screening failures:

- Date of informed consent(s).
- Date of screening failure.
- Reason for screening failure.
    a. Failure to meet eligibility criteria and which eligibility criterion(ia) was (were) not met.
    b. Withdrawal by subject.
    c. Lost to follow-up.

d. Other (if other, a specification should be provided).

- Demographics (full date of birth [day, month, and year], only month and year, or only year as per local legislation, age, sex, race, ethnicity as per local legislation).
- Any (S)AEs.

Any SAE will require expedited reporting as described in Section 13.4.

Re-screening of screening failures (subjects who did not meet the eligibility criteria for participation in the trial) is not allowed. However, if the reason for screening failure is administrative and not due to the subject not meeting the eligibility criteria (e.g. delayed test results or temporary site closure due to the COVID-19 pandemic), re-screening may be permitted. This will require approval by the sponsor's medical expert after thorough review of data from the original screening visit in the eCRF. Subjects to be re-screened must sign a new ICF. Re-screened subjects will get a new subject ID. In addition, the subject ID from the previous screening will be recorded in the eCRF.

9 Treatments

9.1 Trial products description

In this trial, the IMPs are (Panel 5):

- LEO 152020 film-coated tablet 50 mg.
- LEO 152020 placebo film-coated tablet.

Panel 5: Identification of investigational medicinal products

Investigational medicinal product	Dosage form	Active ingredient and concentration	Manufacturer responsible for batch release
LEO 152020 film-coated tablet 50 mg	Film-coated tablet	CCI [redacted]	LEO Pharma
LEO 152020 placebo film-coated tablet	Film-coated tablet	Not applicable	LEO Pharma

CCI [redacted]

Composition of LEO 152020 film-coated tablet 50 mg is described in the investigator's brochure. LEO 152020 placebo film-coated tablet contains the same ingredients as LEO 152020 film-coated tablet, except the active ingredient LEO 152020.

9.2 Administration of the investigational medicinal product

General

The IMP will be dispensed to the subject according to the schedule of trial procedures (Section 4). Dispensing of the IMP will be handled by an IRT system. At each dispensing visit, the IRT system will assign any required kit number(s) to the subject.

From baseline to Week 16, the subject will be asked to self-administer the IMP at the trial site or at their home. The subject will self-administer their first dose of IMP at the site and their last dose of IMP at home, in the evening before the Week 16 visit. At the Week 16 visit or the last visit in the trial, the investigator or site staff should confirm with the subject the date and time of last dose of IMP and record the information in the eCRF.

Every day between baseline and Week 16, the subject will be asked to take [redacted] tablets of IMP: [redacted] tablets in the CCI [redacted] and [redacted] tablets in the CCI [redacted] (Panel 6). Administration of the IMP will be explained to the subject in separate instructions for use in their language.

Administration of the IMP at the trial site

At the visits indicated in the schedule of trial procedures (Section 4), the subject will be asked to self-administer the IMP at the trial site under the supervision of the site staff. At baseline, the subject will self-administer the first dose of IMP at the site. At trial visits from Week 1 to Week 14, the subject will self-administer their morning dose of IMP at the site. The subject will be asked to come fasted to the trial site, i.e. arrive at the site minimum 2 hours after their last meal.

Visits should be scheduled at times to make

- Fasted state and minimum time of [redacted] hours between consecutive doses of IMP feasible for the subject.
- ECG measurement(s) and PK blood sampling feasible for the site staff (see Section 4 [Panel 2 and Panel 3], Sections 11.4.3 and 11.6.1).

At each visit from Week 1 to Week 14 before the subject self-administers the IMP, the site staff should check if the subject is fasted (i.e. arrived at the trial site minimum 2 hours after their last meal) and when they took their last dose of IMP and follow the flowcharts provided in Appendix 7.

Reporting in eCRF

It will be recorded in the eCRF if the subject was fasted (i.e. had arrived at the trial site minimum 2 hours after their last meal).

Administration of the IMP at the subject's home

The subject will be instructed to take [redacted] doses of IMP [redacted] hours apart and no less than [redacted] hours apart.

If the subject misses a dose of IMP at home

If the subject misses a dose of IMP at home, they will be instructed to proceed as follows:

- If at the time the subject becomes aware of the missed dose of IMP, there are **more** than [redacted] hours to the next planned dose, the subject should take the missed dose as soon as they become aware.
- If at the time the subject becomes aware of the missed dose of IMP, there are **less** than [redacted] hours to the next planned dose, the subject should skip the missed dose and wait until the next planned dose of IMP.

If the subject misses a visit or a dose of IMP at the trial site
If the subject misses a visit or a dose of IMP at the trial site, they will be instructed to maintain their dosing schedule and, if possible, to take the missed dose of IMP at their home instead (Panel 20).

Precautions pre- and post-dose of IMP at the trial site
ECGs will be measured pre- and/or post-dose of IMP (Section 11.4.3).

Provisions for overdose
The risk of accidental overdose with a clinical consequence is considered low as it would involve intake of an unlikely large dose of IMP at once: CCI mg in a single dose (39). This is equivalent to CC tablets in the LEO 152020 CCI treatment group where the highest exposure is expected.

To minimize the risk of accidental overdose, site staff should explain to the subject how to self-administer the IMP and instructions for use will be given to the subject to take home. For more information about medication errors, including accidental overdose, see Section 13.6.2.

There are no available data on overdose with LEO 152020. LEO Pharma does not recommend any specific treatment in relation to overdose. It will be at the discretion of the investigator to take appropriate action to treat and follow up on any accidental overdose.

9.3 Treatment assignment and blinding

9.3.1 Treatment assignment

Subjects who comply with all eligibility criteria (Sections 8.1 to 8.3) will be randomized to 1 of the following oral treatments:

- LEO 152020 CCI
- LEO 152020 CCI
- LEO 152020 CCI
- Placebo CCI .

Within the strata defined by baseline disease severity (EASI at baseline) and region (Japan, non-Japanese countries), subjects will be randomized in a 4:3:3:4 ratio, using a permuted block design. Approximately 30% subjects with EASI between 7.1 and 16 at baseline (7.1≤ EASI ≤16) and 70% subjects with EASI between 16.1 and 50 at baseline (16.1≤ EASI ≤50) will be randomized in the trial.

The IRT system will be used to control randomization and to track stratification and IMP supply chain and expiry.

9.3.2 Blinding

Triple blinding (subject, investigator, and assessor of the data/study outcome [sponsor]) from randomization to formal unblinding of the trial will be applied.

Investigational medicinal product
The packaging and labelling of the IMPs will contain no evidence of their identity.
LEO 152020 film-coated tablets 50 mg and LEO 152020 placebo film-coated tablets have been designed to look alike (same size and color) and telling them apart by sensory evaluation is not considered possible.

To ensure blinding across all treatment groups, subjects will be asked to take CCI tablets of IMP daily: CCI tablets in the CCI and CCI tablets in the CCI (Section 9.2) as described in Panel 6.

Panel 6: Dosing schedule and treatment composition in each treatment group

Treatment group	CCI dose of IMP		CCI dose of IMP	
	LEO 152020 film-coated tablet **50 mg**	LEO 152020 **placebo** film-coated tablet	LEO 152020 film-coated tablet **50 mg**	LEO 152020 **placebo** film-coated tablet
LEO 152020 CCI	CCI			
LEO 152020 CCI				
LEO 152020 CCI				
Placebo CCI				

Abbreviations: IMP = investigational medicinal product.

To avoid medication errors in the LEO 152020 CCI treatment group and to ensure blinding across all treatment groups, the CCI doses of IMP must clearly be identified on the packaging for all treatment groups. Packaging and labelling of the IMPs is described in more detail in Section 9.8.1.

Safety
During trial conduct, unblinding of an individual subject for emergency or regulatory purposes (SUSAR reporting) may be necessary. In such cases, unblinding will strictly be limited to the individual(s) needed to conduct the unblinding procedure. No unblinded safety data will be shared with the rest of the clinical team before DBL. For more information about emergency unblinding, see Section 9.3.3.

Subject safety and overall trial conduct will be monitored by an external unblinded DMC not involved in trial conduct as described in a separate DMC charter (see also Appendix 3H). In their interactions with the sponsor, the DMC will not share unblinded data.

Pharmacokinetics and pharmacodynamics
PK and PD samples will be collected for all subjects as part of the general blood work in the trial. Skin biopsies are an optional component of the trial and will be collected for a subgroup of subjects randomly and without knowledge of treatment allocation (Section 11.7.3).

PK blood samples of subjects treated with LEO 152020 will be analyzed by an external unblinded, specialized laboratory not involved in trial conduct. During the trial, raw PK data will be reviewed by an unblinded monitoring scientist at the sponsor to ensure data quality. In this context, unblinding means knowing the link between subject ID and treatment allocation only. No unblinded PK data will be shared with the clinical team at the sponsor before DBL.

All PD blood samples and skin biopsies will be analyzed by an external unblinded, specialized laboratory not involved in trial conduct. No unblinded PD data will be shared with the sponsor clinical team before DBL.

Data monitoring
Until DBL, data monitoring at the sponsor will be conducted on blinded data.

9.3.3 Emergency unblinding of individual subject treatment

While safety of the subject always comes first, it is still important to carefully consider if unblinding is necessary to ensure subject safety. An emergency unblinding request can be made by the investigator, HCPs who are not members of the site staff, or authorized LEO Pharma personnel.

Provisions are in place for 24-hour emergency unblinding of individual subject treatment. If emergency unblinding is required, the investigator can unblind a subject's treatment via the unblinding IRT system or unblinding CRO.

For a requester who is not a member of the site staff and who does not have access to the IRT system (e.g. a physician in an emergency room), a local contact number for the emergency unblinding CRO will be provided on the subject card (Appendix 3B) to be used if the investigator or delegated site staff cannot be reached. In such case, the requester will provide the trial ID and subject ID to the emergency unblinding CRO who will immediately reveal the individual treatment allocation.

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

9.4 Background treatment

The subject will be asked to apply an emollient on lesional and non-lesional skin from Week -1 to Week 16.

In the run-in period (Week -1 to baseline), the subject should apply the emollient at least twice daily for at least 7 consecutive days immediately prior to randomization.

In the treatment period (baseline to Week 16), the subject will be asked to apply the emollient as needed.

In the safety follow-up period (Week 16 to Week 17), the subject may continue applying the emollient as needed.

The emollient should preferably be a basic, bland, additive-free emollient. The emollient should preferably not contain additives such as ceramide, hyaluronic acid, urea, polidocanol, or filaggrin. To ensure use of a suitable emollient, the investigator should provide guidance to the subject as to which locally available emollient to use.

The function of the emollient is to:

- Keep the subject's skin well-moisturized in the absence of systemic and/or topical AD treatment(s) in the run-in period (Week -1 to baseline) and the safety follow-up period (Week 16 to Week 17).
- Act as a complement to systemic treatment with the IMP (standard of care) and keep the subject's skin well-moisturized in the treatment period (baseline to Week 16).

9.5 Rescue treatment

If medically necessary (i.e. to control intolerable worsening of AD symptoms), rescue treatment of AD may be provided to the subject at the discretion of the investigator. If possible, the investigator should attempt to limit the first step of rescue treatment to topical treatment and escalate to systemic treatment if the subject does not respond adequately to topical rescue treatment.

Topical rescue treatment
In this trial, topical rescue treatment of AD consists of TCS and TCI. Subjects provided with topical rescue treatment between first dose of IMP and Week 16 may continue treatment with the IMP and remain in the trial with no change to the visit schedule nor trial assessments/procedures.

Systemic rescue treatment.
If the subject is provided with systemic rescue treatment of AD at any time during the treatment period, treatment with IMP will immediately and permanently be discontinued (see also Section 9.7 for prohibited medications).

Before administering topical or systemic rescue treatment, the investigator may conduct efficacy and safety assessments (e.g. disease severity scores [EASI, vIGA-AD, and SCORAD], AEs, safety laboratory samples, PK blood sample, and concomitant medications/concurrent procedures). However, to safeguard subject safety and well-being, the assessments should only be conducted if the subject's health permits. To further attend to subject safety and well-being, an unscheduled visit , scheduled earlier than the next planned visit, may be arranged to administer the topical or systemic rescue treatment.

If the subject is permanently discontinued from IMP due to use of systemic rescue medication, every effort must be done to monitor the subject as described in Section 10.3.

9.6 Concomitant medications and concurrent procedures

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

- Medication name or therapy (generic or brand name).
- Whether the medication or therapy is a rescue medication for AD. In case of rescue medication for AD, a specification of the reason for lack of efficacy of the IMP should be provided:
  - Lack of efficacy on itch.
  - Lack of efficacy on visible AD symptoms.
  - Lack of efficacy on both itch and visible AD symptoms.
  - Other (if other, a specification should be provided).
- Indication.
- Start and stop dates of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose per administration, unit, and frequency.
- Route of administration: oral, cutaneous, subcutaneous, transdermal, ophthalmic, intramuscular, respiratory (inhalation), intralesional, intraperitoneal, nasal, vaginal, rectal, intravenous, or other (if other, a specification should be provided).

Any concurrent procedure conducted within 3 months prior to screening must be recorded in the subject's medical record and the eCRF with details such as:

- Procedure name (including anatomical area, if relevant).
- Indication.
- Start and stop dates (it will also be recorded if the procedure is ongoing).

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care, at their discretion. Concomitant medication for conditions other than AD (except prohibited medications) may be continued during the trial without dosage change whenever possible.

9.7 Prohibited medications and procedures

The medications and procedures listed in Panel 7 and Appendix 8 are prohibited during the trial. Prohibited medications and procedures prior to and during screening are also listed in Section 8.3.

If prohibited medications are used during the trial, they must be recorded as concomitant medication in the eCRF (Section 9.6).

Prohibited topical medications used as rescue treatment of intolerable AD symptoms are allowed (Section 9.5). Such use of prohibited topical medications does not constitute a protocol deviation.

Panel 7: Prohibited medications and procedures

Medication	Prohibited from	Prohibited to
Allergen immunotherapy	Within 5 half-lives prior to baseline	Week 17 (safety follow-up)
H4R antagonist (oral)	Within 6 months prior to baseline (exclusion criterion 3)	Week 17
Immunoglobulin or blood product	Within 5 half-lives prior to baseline	Week 17
Investigational agents other than LEO 152020	Within 4 weeks or 5 half-lives prior to baseline, whichever is longer	Week 17
Live (attenuated) vaccine	Baseline	Week 17
Medication for which CCI is a known side effect	Within 5 half-lives prior to screening	Week 17
Medications known to inhibit the CCI CCI [a]	Within 5 half-lives prior to baseline	Week 17
Medications known to inhibit the CCI CCI [b]	Within 5 half-lives prior to baseline	Week 17
Medications known to inhibit the CCI CCI [c]	Within 5 half-lives prior to baseline	Week 17
Retinoids	Within 4 weeks prior to baseline	Week 17
Systemic AD treatments	Within 4 weeks or 5 half-lives prior to baseline, whichever is longer	Week 17

Medication	Prohibited from	Prohibited to
Systemic anti-histamines [d]	Within 4 weeks or 5 half-lives prior to baseline, whichever is longer	Week 17
Systemic corticosteroids [e]	Within 4 weeks or 5 half-lives prior to baseline, whichever is longer	Week 17
Systemic immunosuppressive/immunomodulatory treatment (e.g. azathioprine, cyclosporine, dupilumab (or other biologics), interferon-gamma, JAK inhibitors, methotrexate, mycophenolate mofetil)	Within 4 weeks or 5 half-lives prior to baseline, whichever is longer	Week 17
TCS/TCI, except if used as rescue treatment	Week -1	Week 16 (end of treatment)
Other topical AD treatments	Week -1	Week 17
Topical antibiotics [f]	Week -1	Week 16
Procedure	**Prohibited from**	**Prohibited to**
Bleach bath	Within 4 weeks prior to baseline	Week 16
UVA, UVA1, UVB, NBUVB, PUVA therapy, other phototherapy, or tanning beds	Within 4 weeks prior to baseline	Week 17

Abbreviations: AD = atopic dermatitis; CCI [redacted]; H4R = histamine receptor 4; JAK = Janus kinase; NBUVB = narrow-band ultraviolet B; CCI [redacted]; CCI [redacted]; PUVA = psoralen + ultraviolet A; CCI [redacted]; TCI = topical calcineurin inhibitor(s); TCS = topical corticosteroid(s); UVA = ultraviolet A; UVA1 = ultraviolet A1; UVB = ultraviolet B.

[a, b, c] See Appendix 8.

[d] Locally-administered anti-histamines (e.g. eye drops, nasal spray) are allowed.

[e] Inhaled or intranasal steroids at doses up to 1 mg prednisone/day are allowed.

[f] Except if used on small lesional areas.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

The IMPs will be packaged in individually numbered kits according to the principles of blinding described in Section 9.3.2 (Panel 6). CCI [redacted] doses of IMP must clearly be identified on the packaging for all treatment groups.

The labelling of IMPs will be in accordance with the EU guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary use, Annex 13 (40), local regulations, and trial requirements. Label text will be translated into local languages as required.

9.8.2 Shipping of trial products

Initial shipment of IMPs for each trial site will be triggered by first subject screened at the site.

9.8.3 Storage of trial products

At the trial site, all LEO Pharma supplied IMPs must be stored in a secure and restricted area under the conditions specified on the label and remain in the original container until dispensed.

At the trial site, the IMP must be stored ≤25°C/77°F and must not be refrigerated nor frozen.

Storage of IMP may be delegated, e.g. to a hospital pharmacy, as locally applicable and must be documented in the site signature and designation of responsibility log.

Temperature of the storage facilities at the trial site should be monitored using 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 conditions and storage facilities should be checked at least every working day.

Damaged IMP should be documented in the IRT system. Damaged IMP may not be dispensed to the subject.

Storage of the IMP at the subject's home will be described in separate instructions for use for the subject to take home.

9.8.4 Accountability of the investigational medicinal products

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

The IMP will be dispensed to the subject using an IRT system. Dispensing of the IMP may be delegated, e.g. to a hospital pharmacy, as locally applicable and must be documented in the Site Signature and Designation of Responsibility Log.

At each visit after baseline, the subject will be asked to return all (partly) used and unused IMP kits. Returned IMP need not be stored at the trial site at the storage temperature specified in Section 9.8.3 but must be stored separately from non-allocated IMP.

All returned IMP kits will fully be accounted for by the site staff in the IRT system (see separate trial product handling manual for more information). The IRT system will also maintain the inventory status of all IMP kits at the trial site (see separate IRT manual for more information on how to update kit status in the IRT system).

All returned IMP tablets will fully be accounted for by the site staff. Documentation of IMP accountability must be kept for the IMP dispensed to each subject randomized in the trial. This documentation must be available during monitoring visits and will be checked by the CRA to verify correct dispensing of the IMPs.

Reporting in eCRF
It will be recorded in the eCRF how many morning doses and how many evening doses of IMP were taken from the dispensed kit.

9.8.5 Treatment compliance

Treatment compliance for IMP taken at the site
Treatment compliance for IMP taken at the site will be accounted for in the eCRF (see reporting in eCRF below).

Treatment compliance for IMP taken at the subject's home
Treatment compliance for IMP taken at the subject's home will be determined based on IMP accountability. At each visit between baseline and Week 16, all returned IMP tablets will fully be accounted for by the site staff (Section 9.8.4). In case of non-compliance with administration of the IMP at the subject's home, the investigator or site staff should remind the subject of the importance of adhering to the dosing schedule.

Reporting in eCRF
It will be recorded in the eCRF if IMP was taken at the site. If not, a reason should be provided. Date and time of IMP administration will also be recorded.

9.8.6 Trial products destruction

All IMP kits ([partially] used and unused) must be returned to the CMO for destruction according to approved procedures and/or local requirements.

Empty kits, i.e. not containing any IMP (only packaging material), may be destroyed at the trial site.

9.9 Provision for subject care following trial completion

To ensure appropriate treatment of the subject after completion of the trial, the subject will be treated at the discretion of the investigator or referred to (an)other physician(s) according to standard practice.

9.10 Reporting product complaints

Any defects or issues with the IMP including use errors and inadequate labelling must be reported to the Quality Department via 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, that has or potentially could have a serious impact on the subject [e.g. SAE]) must be reported to the Quality Department via Global Safety within 24 hours of knowledge.

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

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

Global Safety, LEO Pharma contact information for reporting product complaints:
E-mail address: drug.safety@leo-pharma.com.
Fax number: +45 7226 3287.

10 Discontinuation and withdrawal

10.1 General principles

If the subject, the investigator, or LEO Pharma considers that it is not in the subject's best interest to continue treatment with the IMP or participate in the trial altogether, a subject may at any time:

- Permanently discontinue IMP (but continue to participate in trial-related activities as described in Section 10.3).
- Or withdraw from the trial (and thereby stop participating in further trial-related activities. Subjects will be encouraged to attend safety assessments to the extent possible to leave the trial in all safety [Section 10.3]).

Subjects who permanently discontinue IMP or withdraw from the trial will not be replaced.

If a subject withdraws from the trial, they may request destruction of any samples taken and not tested. The investigator must document this in the subject's medical record and inform LEO Pharma.

10.2 Reasons for permanent discontinuation of investigational medicinal product

Subjects will permanently discontinue IMP in the event of:

- Evidence of pregnancy.
- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.
- Initiation of systemic rescue treatment of AD.
- Initiation of prohibited medication (except topical medications used as rescue treatment of AD) which cannot be safely replaced by other non-prohibited medications.
- QTcF >500 ms or increase in QTcF from baseline >60 ms.
- Other reasons, at the discretion of the investigator. If other, a specification should be provided.

Reporting in eCRF
The primary reason for permanent discontinuation of IMP must be recorded in the subject's medical record and on the end of treatment form in the eCRF where the following options are available:

- Death.
- Pregnancy.
- Adverse event (if adverse event, a specification must be provided).
- Lack of efficacy. If lack of efficacy, a specification of the reason for lack of efficacy of the IMP must be provided:
  - Lack of efficacy on itch.
  - Lack of efficacy on visible AD symptoms.
  - Lack of efficacy on both itch and visible AD symptoms.
  - Other (if other, a specification must be provided).
- Withdrawal by subject.
- Lost to follow-up.
- Other (if other, a specification must be provided).

In case the primary reason is adverse event, the AE in question will be linked to the permanent discontinuation of IMP. To support the statistical analysis, it will also be recorded if the permanent discontinuation of IMP was due to the COVID-19 pandemic.

For reasons for withdrawal from the trial, see in Section 11.8, End of trial form.

10.3 Early termination assessments

Assessments/procedures to be conducted at the visits below are listed in the schedule of trial procedures (Section 4).

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

- An early termination visit as soon as possible after last dose of IMP.
- The primary endpoint visit (nominal), 16 weeks after first dose of IMP.

See also Section 10.4 for the continued assessment of discontinued subjects.

Withdrawal from trial
Subjects who withdraw from the trial prior to randomization will be considered screening failures

Subjects who withdraw from trial after randomization will be asked to attend:

- An early termination visit as soon as possible after last dose of IMP.
- A safety follow-up visit (7 days after last dose of IMP).

A subject, who at the earliest can come to the early termination visit 3 days after last dose of IMP or later, should only be asked to attend the early termination visit.

If the subject agrees, the investigator will review any AEs which will be followed up as described in Section 13.7.

10.4 Continued assessment of subjects after permanent discontinuation of investigational medicinal product

Subjects who permanently discontinue IMP prior to Week 16 should be encouraged to continue participating in the trial and to follow their visit schedule to the extent possible.

10.5 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 them.

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

- The trial site must attempt to contact the subject and reschedule the missed visit as soon as possible and remind the subject of the importance of respecting the visit schedule. The trial site should also ascertain whether the subject wishes to continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent method[s]). 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

Assessments and procedures to be conducted at each visit are listed in the schedule of trial procedures (Section 4). At visits with ECG measurement(s) and/or PK blood sample(s), the sequence of assessments presented in Panel 3 must be followed.

Subjects will be under the careful supervision of a principal investigator who must be a dermatologist or allergist. Investigators must be physicians and have experience in treating atopic dermatitis as well as documented experience with and/or training in the assessments used in the trial. In the US, advanced registered nurses may be investigators (but not principal investigators).

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

11.2 Screening/baseline assessments

11.2.1 Demographics

The following demographic data will be recorded at screening (Section 4):

- Full date of birth (day, month, and year) or partial date of birth (only month and year), or only year, as per local legislation.
- Age (as on the day informed consent is signed, if full date of birth cannot be collected due to local legislation).
- Sex (female, male).
- Ethnic origin (self-reported by the subject, Hispanic or Latino, not Hispanic or Latino), as allowed by local legislation.
- Race: American Indian or Alaska native, Asian, Asian Japanese, Black or African American, native Hawaiian or other Pacific islander, White, other (if other, a specification should be provided).

At baseline, only age will be recorded on the randomization form (Section 4).

11.2.2 Body measurements (height and weight)

Height and weight will be recorded according to the schedule of trial procedure (Section 4). The subject's height (without shoes) and the subject's weight (in indoor clothing and without shoes) will be measured.

11.2.3 Medical history

Medical history will be recorded according to the schedule of trial procedures (Section 4).

Atopy history (age at onset of AD, and previous AD treatments) as well as other relevant medical and surgical history, including concurrent diagnoses within 12 months prior to baseline, will be recorded. For each condition, surgical procedure, or diagnosis, the start and stop dates will be recorded. It will also be recorded if the condition or diagnosis is ongoing.

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

11.2.4 Body surface area involvement

BSA affected by AD will be assessed according to the schedule of trial procedures (Section 4) as component A of SCORAD (see Section 11.3.3).

11.2.5 Other screening assessments

Hepatitis B and C, and HIV testing will be conducted according to the schedule of trial procedures (Section 4). Tuberculosis testing will be per local standard of care (see exclusion criterion 8). If the tuberculosis test cannot be analyzed locally, it should be sent to the central laboratory.

11.3 Efficacy assessments

11.3.1 Eczema Area and Severity Index (EASI)

EASI will be assessed by the investigator 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.

EASI is a composite score ranging from 0 to 72 with higher scores indicating a more severe or more extensive condition. The score will be calculated as described in Panel 8. Briefly, the investigator will assess the severity of 4 AD disease characteristics (erythema, induration/papulation, excoriation, and lichenification) on the 4 body regions (head/neck, trunk, upper extremities, and lower extremities). Severity will be assessed using the severity score scale presented in Panel 9. For each body region, a severity sum score will be calculated and multiplied by an area score (Panel 9) and a weighting factor. The EASI score equals the sum of scores obtained for each body region (Panel 8) (41).

Reporting in eCRF

The body region, severity of the disease characteristics (erythema, induration/papulation, excoriation, and lichenification), and the area score will be recorded in the eCRF.

Panel 8: Calculation of the Eczema Area and Severity Index (EASI)

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

Abbreviations: AS = area score; EASI = Eczema Area and Severity Index; SS = severity score.
Modified from (42).

Panel 9: Eczema Area and Severity Index (EASI) severity score scale and area score scale

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

[a] Half-score 0.5 is not allowed. Half-scores 1.5 and 2.5 are allowed (42).

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

11.3.2 Validated Investigator Global Assessment Scale for Atopic Dermatitis (vIGA-AD)

vIGA-AD will be assessed by the investigator according to the schedule of trial procedures (Section 4). vIGA-AD is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Panel 10) (43). 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.

Reporting in eCRF

The disease severity score will be recorded in the eCRF.

Panel 10: Validated Investigator Global Assessment Scale for Atopic Dermatitis (vIGA-AD)

Score	Morphological description
0 - Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 - Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 - Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 - Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 - Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing and crusting may be present.

11.3.3 Scoring Atopic Dermatitis (SCORAD)

SCORAD will be assessed by the investigator 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.

SCORAD scores range from 0 to 103 with higher scores indicating a more severe or more extensive condition. The assessment consists of 3 components: A=extent, B=intensity, and C=subjective symptoms (44).

Extent (A)
The extend of AD will be assessed by the investigator for each body region (the numbers in brackets indicate the highest possible score for each region): head and neck (9%), anterior trunk (18%), back (18%), upper limbs (18%), lower limbs (36%), and genitals (1%). The extend of AD is the sum of scores of all body regions and the maximum score is 100%.

Intensity (B)
The intensity of 6 specific symptoms of AD (erythema, edema/papulation, oozing/crusting, excoriation, lichenification, and dryness) will be assessed by the investigator. The first 5 symptoms will be assessed on an average representative area using the following scale:

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

Dryness will be assessed on non-lesional skin.

The intensity score is the sum of intensity scores of the 6 symptoms and the maximum score is 18.

Subjective symptoms (C)
Average itch and sleeplessness over the last 3 days/nights will be assessed by the subject on a visual analogue scale, where 0 means no itching (or no trouble sleeping) and 10 means unbearable itching (or a lot of trouble sleeping). The subjective symptom score is the sum of the itch and sleeplessness scores and the maximum score is 20.

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

Reporting in eCRF
Components A, B, and C will be recorded in the eCRF.

11.3.4 Atopic Dermatitis Symptom Diary (ADSD, eDiary)

ADSD is considered a subject's assessment of efficacy. ADSD is a 9-item sign and symptom diary developed by LEO Pharma. It assesses the severity of CCI [redacted]. The subject assesses the severity of each symptom 'at its worst' over the past 24 hours using an 11-point NRS, with anchors at 0='no [symptom]' and 10='worst possible [symptom]'.

From Week -1 to Week 16, ADSD will be completed by the subject on the eDiary daily. An overview of all PROs, including other PROs collected in the eDiary and PROs collected at the trial site, is presented in Section 11.5.1.

11.4 Safety assessments

11.4.1 Vital signs

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

If a subject presents with an abnormal vital sign, the measurement of the vital sign can be repeated approximately 2-5 minutes later to verify the first measurement. Should the repeated measurement result in a normal value, the measurement must be repeated once more. If the third measurement verifies the second (normal) value, the first measurement should be considered false and the third measurement should be recorded in the eCRF. If the third measurement confirms the first (abnormal) value, the second measurement should be considered false and the third measurement should be recorded in the eCRF. Only the last measurement considered true should be recorded in the eCRF.

In case of an abnormal clinically significant vital sign at screening and/or baseline, it will be at the discretion of the investigator if the subject should be randomized in the trial in accordance with exclusion criterion 18. During the trial, if a subject presents with an abnormal clinically significant vital sign, the investigator must take appropriate action, at their discretion.

Reporting in eCRF
Vital signs will be recorded in the eCRF and if not measured, a reason should be provided.

Abnormal clinically significant vital signs at screening and baseline will be documented as medical history in the eCRF. At subsequent visits, any new abnormal clinically significant vital signs, symptoms, or illnesses, as well as any clinically significant deterioration of a pre-existing condition after randomization will be reported as an AE as described in Section 13.3.

11.4.2 Physical examination

A physical examination of the subject including general appearance, regional lymph nodes, and dermatologic examination must be conducted according to the schedule of trial procedures (Section 4). If clinically indicated, ad hoc physical examination may be conducted at any time during the trial.

In case of an abnormal clinically significant finding during physical examination at screening and/or baseline, it will be at the discretion of the investigator if the subject should be randomized in the trial in accordance with exclusion criterion 18. During the trial, if a subject presents with an abnormal clinically significant finding during physical examination, the investigator must take appropriate action, at their discretion.

Reporting in eCRF
It will be recorded in the eCRF if a physical examination was conducted. If not, a reason should be provided. The investigator's evaluation of the physical examination (normal, abnormal not clinically significant, abnormal clinically significant) will also be recorded.

Abnormal clinically significant findings during physical examination at screening and baseline except findings related to AD will be documented as medical history in the eCRF. At subsequent visits, any new abnormal clinically significant findings, symptoms, or illnesses, as well as any clinically significant deterioration of a pre-existing condition after randomization will be reported as an AE as described in Section 13.3.

11.4.3 Electrocardiography

ECGs must be measured according to the schedule of trial procedure and special attention should be paid to timing of measurements (see Section 4, Panel 2 and Panel 3, for more information). 12-lead resting digital ECGs will be recorded after the subject has been in supine position for at least 5 minutes.

At an unscheduled visit, it will be at the discretion of the investigator if an ECG should be measured.

The investigator must evaluate each ECG for immediate subject safety and date and sign their evaluation. In case of a suspected abnormal ECG, the investigator must take appropriate action, at their discretion.

All ECG data will be transferred to a central ECG service company for central evaluation. At the service company, a cardiologist will analyze and interpret the ECG data and provide ECG evaluation reports to the trial sites.

The investigator must review the ECG reports and evaluate all abnormal ECGs (clinically significant or not clinically significant). The investigator must document their review by signing the ECG reports at the trial site. The investigator is ultimately responsible for judging the clinical significance of any abnormal ECG. However, CCI >450 ms (men) and CCI >460 ms (women) are considered clinically relevant CCI and should therefore be reported as AEs as described in Section 13.6.1.

If a subject presents with a **severe** CCI, i.e. CCI >500 ms or an increase in CCI from baseline >60 ms, the ECG should be repeated. If the CCI or increase in CCI from baseline is confirmed:

- A PK sample (if not already planned at the visit) must be taken close to the last measured ECG.
- The subject must permanently be discontinued from IMP.

If the subject presents with a **moderate** CCI, i.e. 480 ms< CCI ≤500 ms or 30 ms< increase in CCI from baseline ≤60 ms, the ECG should be repeated. If the CCI or increase in CCI from baseline is confirmed:

- A PK sample (if not already planned at the visit) must be taken close to the last measured ECG.
- A post-dose ECG and post-dose PK sample must be taken as described in Panel 3 for Week 1 at every visit onwards and as long as the subject presents with the moderate QT prolongation.

If the subject returns to CCI ≤480 ms (mild CCI or normal CCI interval) and increase in CCI from baseline ≤30 ms, the ECG and PK monitoring schedule described in Section 4 should be followed again.

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

Reporting in eCRF
It must be recorded in the eCRF if an ECG was measured. If not, a reason must be provided. It will also be recorded if the subject was fasted (i.e. had arrived at the trial site minimum 2 hours after their last meal). The investigator's evaluation of ECG result (normal, abnormal not clinically significant, abnormal clinically significant) must also be recorded.

Before first dose of IMP, any abnormal clinically significant or clinically relevant ECG finding will be documented as medical history in the eCRF. After first dose of IMP, any new abnormal clinically significant or clinically relevant ECG finding, symptoms, or illnesses, as well as any clinically significant deterioration of a pre-existing condition will be reported as an AE as described in Section 13.3.

11.4.4 Laboratory testing

11.4.4.1 Overview

Blood and urine samples will be collected according to the schedule of trial procedures (Section 4) and the evaluations listed in Panel 11 will be conducted by the central laboratory.

Panel 11: Clinical laboratory tests

Clinical chemistry	Hematology
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bilirubin Calcium Cholesterol LDL cholesterol HDL cholesterol Creatinine Gamma glutamyl transferase Magnesium Potassium Protein Sodium Urea nitrogen	Basophils Eosinophils Hematocrit Hemoglobin Leukocytes Lymphocytes Monocytes Neutrophils Thrombocytes
Serology	**Tuberculosis test**
Hepatitis B virus core antibody Hepatitis B virus surface antibody Hepatitis B virus surface antigen Hepatitis C virus antibody HIV-1 antibody HIV-2 antibody	Per local standard at screening (see exclusion criterion 8)
Urinalysis	**Pregnancy test [a]**
Glucose Ketones Leukocytes Nitrite Occult blood Protein	Choriogonadotropin beta Urine pregnancy test [b]

Abbreviations: HDL = high density lipoprotein; HIV = human immunodeficiency virus; LDL = low density lipoprotein.

[a] Women of childbearing potential only.

[b] A positive urine pregnancy test must be verified with a serum pregnancy test.

11.4.4.2 Investigator evaluation of laboratory samples

Laboratory samples sent to the central laboratory
Clinical chemistry, hematology, serology, and urinalysis will be analyzed by a central laboratory which will provide results to the trial sites. Laboratory parameters will be classified as low, normal, or high, depending on whether the value is below, within, or above the reference range. The investigator must evaluate all results outside the reference range (clinically significant or not clinically significant) and sign and date their evaluation which will be archived in the investigator's trial file.

In case of an abnormal clinically significant laboratory result at screening and/or baseline, it will be at the discretion of the investigator if the subject should be randomized in the trial in accordance with exclusion criterion 18. During the trial, if a subject presents with an abnormal clinically significant laboratory result, the investigator must take appropriate action, at their discretion.

In case additional analyses are needed to support interpretation of a positive test result for Hepatitis B, Hepatitis C, or HIV, these will be conducted by the central laboratory. Subjects with a positive serology or tuberculosis test at screening should be referred to a competent health care structure for treatment and follow-up.

Serum pregnancy tests for women of childbearing potential will be analyzed by a central laboratory which will provide results to the trial sites.

Instruction for collection, processing, storage, and shipment of laboratory samples, as well as laboratory contact information specific to this trial will be provided in a separate laboratory manual.

Laboratory tests conducted at the trial site
Subjects with a positive tuberculosis test conducted at the trial site at screening should be referred to a competent health care structure for treatment and follow-up.

Urine samples will be tested with a dipstick at the trial site. It will be at the discretion of the investigator if a urine sample should be sent to the central laboratory for further analysis.

Urine pregnancy tests for women of childbearing potential will be conducted at the trial sites. A positive urine pregnancy test must be verified with a serum pregnancy test.

Reporting in eCRF
It will be recorded in the eCRF if a blood sample was collected. If not, a reason should be provided. The investigator's assessment of the results (normal, abnormal not clinically significant, abnormal clinically significant) will also be recorded.

It will be recorded in the eCRF if a urine sample was tested with a dipstick. If not, a reason should be provided. It will be recorded if the urine sample was sent to the central laboratory for further analysis (urinalysis). In case urinalysis is conducted, the investigator's assessment of the results (normal, abnormal not clinically significant, abnormal clinically significant) will also be recorded.

It will be recorded in the eCRF if the subject is a woman of childbearing potential and if a urine pregnancy test was conducted. If not, a reason should be provided. The date and outcome (positive, negative) of the urine pregnancy test will also be recorded.

Abnormal clinically significant laboratory results at screening, Week -1, and baseline will be documented as medical history in the eCRF. At subsequent visits, any new abnormal clinically significant laboratory results, symptoms, or illnesses, as well as any clinically significant deterioration of a pre-existing condition after randomization will be reported as an AE as described in Section 13.3.

11.5 Patient-reported outcomes

11.5.1 Overview

During the trial, the subject will be asked to assess their perception of AD by means of PROs. PROs considered subject assessment of efficacy are described in Section 11.3.4. Other PROs used in the trial are described in the subsections below.

At the screening visit, subject eligibility to participate in the trial must be confirmed before any PROs are completed.

At Week -1, the subject will receive an eDiary and training in using the device. From Week -1 to Week 16, the subject will be asked to complete the eDiary twice daily once in the morning and once in the evening as described below. The following PROs will be completed in the morning:

- Nocturnal CCI (Section 11.5.2).
- Difficulty CCI (Section 11.5.3).
- Frequency of CCI During the Night (Section 11.5.4).
- CCI (Section 11.5.5).
- CCI (Section 11.5.6).

ADSD (all components, see Section 11.3.4) will be completed in the evening.

Between Week -1 and Week 16, an automatic alarm will inform the investigator/site staff about non-compliance with eDiary completion. In case of non-compliance, the investigator should remind the subject of the importance of completing the eDiary daily.

Subjects will be asked to return the eDiary at Week 16 or at their last visit in the trial.

The subject will be asked to complete the following PROs on an electronic device at the trial site according to the schedule of trial procedures (Section 4):

- POEM.
- DLQI.
- EQ-5D-5L.
- WPAI:AD.
- HADS.
- PGI-S
    - ADSD.
    - CCI
    - Nocturnal CCI
    - Difficulty CCI.
    - Frequency of CCI During the Night.

- CCI
- CCI

- PGI-C
  - ADSD.
  - CCI
  - Nocturnal CCI
  - Difficulty CCI
  - Frequency of CCI During the Night.
  - CCI
  - CCI

11.5.2 Nocturnal CCI (eDiary)

Nocturnal CCI is a single item questionnaire designed to assess how much the subject CCI during the past night. It will be assessed on a 6-point categorical scale (‘none of the night’, ‘a little of the night’, ‘some of the night’, ‘a lot of the night’, ‘all of the night’, ‘I don't know’). The subject will be asked to assess Nocturnal CCI in the eDiary daily.

11.5.3 Difficulty CCI (eDiary)

Difficulty CCI is a single item questionnaire designed to assess the subject’s difficulty CCI the past night. It will be assessed on a 5-point categorical scale (‘not difficult’, ‘a little difficult’, ‘moderately difficult’, ‘extremely difficult’, ‘I don’t know’). The subject will be asked to assess Difficulty CCI in the eDiary daily.

11.5.4 Frequency of CCI During the Night (eDiary)

Frequency of CCI During the Night is a single item questionnaire designed to assess how many times the subject CCI the past night. It will be assessed on a 5-point categorical scale (‘not at all’, ‘CCI 1 time’, ‘CCI 2 times’, ‘CCI 3 times or more’, ‘I don’t know’). The subject will be asked to assess Frequency of CCI CCI During the Night in the eDiary daily.

11.5.5 CCI , eDiary)

CCI is a single item questionnaire designed to assess for how long the subject was CCI . It will be assessed on a 7-point categorical scale ('I did not CCI ', '30 minutes or less', 'more than 30 min but less than 1 hour', 'more than 1 hour but less 2 hours', 'more than 2 hours but less than 3 hours', '3 hours or more', 'I don't know'). The subject will be asked to assess CCI in the eDiary daily.

11.5.6 CCI (eDiary)

CCI is a single item questionnaire designed to assess how much of the CCI CCI . It will be assessed on 6-point categorical scale ('none of the CCI 'a little of the CCI 'some of the CCI 'a lot of the CCI 'all of the CCI 'I don't know'). The subject will be asked to assess CCI in the eDiary daily.

11.5.7 Patient-Oriented Eczema Measure (POEM, at trial site)

POEM consists of 7 items, each addressing a specific symptom (itching, sleep, bleeding, weeping, cracking, flaking, and dryness). The subject will be asked to score how often they experienced each symptom over the past week on a 5-point categorical 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 (0 to 28) is the sum of the 7 items and reflects disease-related morbidity with higher scores indicating more severe symptoms (45). The subject will be asked to complete POEM on an electronic device at the trial site according to the schedule of trial procedures (Section 4).

11.5.8 Dermatology Life Quality Index (DLQI, at trial site)

DLQI 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 past week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment. Each item will be 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 (0 to 30) is the sum of the 10 items with higher scores indicating a poorer quality of life (46). The subject will be asked to complete DLQI on an electronic device at the trial site according to the schedule of trial procedures (Section 4).

11.5.9 EuroQol 5-Dimension Health Questionnaire 5 Level (EQ-5D-5L, at trial site)

EQ-5D-5L is a self-administered questionnaire used to assess health status 'today' and is divided into 2 sections. The first section includes 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Each dimension is assessed using a 5-point categorical 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') (47). The subject will be asked to complete EQ-5D-5L on an electronic device at the trial site according to the schedule of trial procedures (Section 4).

11.5.10 Work Productivity and Activity Impairment: Atopic Dermatitis (WPAI:AD, at trial site)

WPAI:AD consists of 6 items and scores can be calculated for 4 domains, each reflecting the percentage impairment due to AD during the past week, with higher scores indicating a greater impairment and lesser productivity (48):

- Absenteeism: percentage work time missed due to AD for those who were employed the past week.
- Presenteeism: percentage impairment while working due to AD for those who were employed and actually worked the past week.
- Work productivity loss: percentage overall work impairment due to AD for those who were employed the past week.
- Activity impairment: percentage activity impairment due to AD for all respondents.

The subject will be asked to complete WPAI:AD on an electronic device at the trial site according to the schedule of trial procedures (Section 4).

11.5.11 Hospital Anxiety and Depression Scale (HADS, at trial site)

HADS is a 14-item questionnaire with scores ranging from 0 to 21 for anxiety and 0 to 21 for depression. Each of the 14 items will be evaluated on a Likert scale. Scores are considered normal from 0 to 7 and abnormal from 11 to 21 and are categorized as: normal (0 to 7), mild (8 to 10), moderate (11 to 14), and severe (15 to 21) (49). The subject will be asked to complete HADS on an electronic device at the trial site according to the schedule of trial procedures (Section 4). If the subject presents with symptoms of clinical depression and/or anxiety, the investigator should take appropriate action at their discretion.

11.5.12 Patient's Global Impression of Severity questionnaires (PGI-S, at trial site)

PGI-S is a single item questionnaire designed to assess the subject's overall perception of severity. In this trial the severity of signs and symptoms of AD, CCI nocturnal CCI difficulty CCI, frequency of CCI during the night, CCI and CCI over the past week will be evaluated. The subject will be asked to choose 1 option from a 4-point categorical scale as described in Panel 12 (50). The subject will be asked to complete the PGI-S questionnaires (ADSD PGI-S, CCI PGI-S, Nocturnal CCI PGI-S, Difficulty CCI PGI-S, Frequency of CCI During the Night PGI-S, CCI PGI-S, CCI PGI-S) on an electronic device at the trial site according to the schedule of trial procedures (Section 4).

Panel 12: Patient's Global Impression of Severity (PGI-S) scales

Patient reported outcome	Scale
ADSD PGI-S CCI PGI-S Nocturnal CCI PGI-S Difficulty CCI PGI-S	'None', 'mild', 'moderate', 'severe'
Frequency of CCI During the Night PGI-S	'Never', 'sometimes', 'often', 'very often'
CCI PGI-S	'None', 'a little', 'some', 'a lot'
CCI PGI-S	'Poor', 'fair', 'good', 'excellent'

Abbreviations: ADSD = atopic dermatitis symptom diary; PGI-S = Patient's Global Impression of Severity; CCI.

11.5.13 Patient's Global Impression of Change questionnaires (PGI-C, at trial site)

PGI-C is a single item questionnaire designed to assess the subject's overall impression of change. In this trial the change in signs and symptoms of AD, CCI nocturnal CCI difficulty CCI frequency of CCI during the night, CCI and CCI since the subject started treatment will be evaluated. The subject will be asked to choose 1 option from a 5-point categorical scale ('much better', 'a little better', 'no change', 'a little worse', 'much worse') (50). The subject will be asked to complete the PGI-C questionnaires (ADSD PGI-C, CCI PGI-C, Nocturnal CCI PGI-C, Difficulty CCI CCI PGI-C, Frequency of CCI During the Night PGI-C, CCI PGI-C, CCI PGI-C) on an electronic device at the trial site according to the schedule of trial procedures (Section 4).

11.6 Pharmacokinetic and pharmacodynamic assessments

11.6.1 Pharmacokinetic assessments

Blood samples for the measurement of LEO 152020 plasma concentration (C_{trough} and C_{max}) will be collected according to the schedule of trial procedures and special attention should be paid to timing of collection (see Section 4, Panel 2 and Panel 3, for more information).

Pre- and post-dose PK blood samples should be collected within 5-10 min after the pre- and post-dose ECGs, respectively (see also Section 11.4.3 for more information about timing for the ECG measurements).

Given the time window for post-dose ECG measurements (1 hour±15 min after dosing), the time window for a post-dose PK blood sample is CCI after dosing.

Instructions for collection, handling, and shipment of PK samples will be provided in a separate laboratory manual.

PK samples of subjects treated with LEO 152020 will be analyzed by an external laboratory using a validated bioanalytical method. The method used to analyze the samples will be described in a separate bioanalytical report appended to the CTR.

Reporting in eCRF

It will be recorded in the eCRF if PK blood samples were collected. If not, a reason should be provided.

11.6.2 Pharmacodynamic assessments

Blood biomarkers
Serum samples for biomarker analysis will be collected according to the schedule of trial procedures (Section 4).

If no efficacy of treatment is observed (no superiority of LEO 152020 vs. placebo), analysis of blood biomarkers may not be carried out since effects of LEO 152020 on molecular markers would in this case not be expected.

Collection, handling, and shipment instructions for serum samples will be provided in a separate laboratory manual.

The biomarker assessments are exploratory in nature and their results will be reported in a separate report appended to the CTR.

Reporting in eCRF
It will be recorded in the eCRF if PD blood biomarker samples were collected. If not, a reason should be provided.

For skin biomarkers, see Section 11.7.3.

11.7 Optional assessments

11.7.1 Overview

Optional assessments are listed in the schedule of trial procedures (Section 4) and described in the subsections below. Participation in these optional components of the trial is not required for participation in the core part of the trial and the subject will be asked to provide additional consent.

The optional assessments are exploratory in nature and their results will be presented in a separate addendum to the CTR.

11.7.2 Wristband scratch and sleep monitoring

Subjects participating in this optional component of the trial will be the first approximately 100 subjects who provide additional consent for this assessment.

At Week -1, the subject will receive 2 wristband actigraphy devices (CCI , CCI) together with instructions for use. From Week -1 to Week 16, the subject will be asked to wear 1 device on each wrist daily and without interruption. If this is too inconvenient, the device worn on the subject's dominant wrist should at least be worn at nighttime during the subject's standard sleep period. If necessary, a hypoallergenic bandage can be placed under each device to prevent skin irritation. The devices are water resistant and do not need to be removed for showering or bathing but should be removed when spending an extended time in the water (e.g. when swimming).

At each visit between Week -1 and Week 16, the subject will be asked to bring the devices back to the site for data transfer using the CCI software. The devices can record 30 days of data at a time. Therefore, the time between consecutives visit should not exceed 30 days and special attention should be paid in case of missed visits.

The wristband actigraphy devices contain a tri-axial accelerometer sampling motion (in units of acceleration, g) at a rate of 20 Hz. Actigraphy data will be processed in Rapid Actigraphy Data Analyzer software CCI). First, the segmentation algorithm (51) will be applied which objectively differentiates active, major rest, minor rest, and missing data periods (during which the device was not worn). Within the major rest periods, which represent time for the main sleep period, the CCI algorithm (52) and sleep/wake algorithm (53) will be applied. The CCI algorithm will quantify individual CCI events used to generate CCI endpoints including the number of events per hour and the duration (in seconds) of events per hour. The CCI algorithm uses movement to estimate CCI versus CCI and will be used generate CCI endpoints including CCI (percentage of the major rest period spent CCI CCI (in minutes), and nocturnal CCI

Reporting in eCRF

At the run-in visit, it will be recorded in the eCRF which hand is the subject's dominant hand and the ID numbers of the wristband actigraphy devices provided to the subject. At each visit between baseline and Week 16, it will be recorded:

- If the subject wore the device as instructed. If not, a reason should be provided.
- If data was transferred from the devices. If not, a reason should be provided.
- If new devices were provided to the subject along with their device ID numbers.

11.7.3 Skin biopsies

Subjects, who have lesions at a location suitable for a biopsy (i.e. ventral arm, ventral forearm, dorsal arm, dorsal forearm, antecubital fossa, trunk, lower limb) will be asked if they agree to provide skin biopsies. Skin biopsies will be collected according to the schedule of trial procedures (Section 4).

Subjects participating in this optional component of the trial will be the first approximately up to 40% of randomized subjects who provide additional consent for this assessment.

A total of 3 skin biopsies (3-mm punch biopsies) will be collected according to the schedule of trial procedures (Section 4):

- 2 at baseline (1 biopsy from lesional skin and 1 biopsy from non-lesional skin).
- 1 at Week 16 (end of treatment) from the same area as where the baseline lesional skin biopsy was taken or from a nearby area.

To minimize discomfort, a local anesthetic should be injected to numb the area where the biopsy will be taken. Subjects who previously have had reactions to anesthetic medication must be excluded from participation in this component of the trial (but may be included in the core part of the trial, provided that they meet all eligibility criteria). A check of wound healing at the biopsy site including removal of sutures, if applicable, will be conducted at the next trial visit according to the schedule of trial procedures (Section 4).

Further instructions for collection, handling, and shipment of skin biopsy samples will be provided in a separate laboratory manual.

Reporting in eCRF
It will be recorded in the eCRF if a biopsy was collected, from which body location it was collected (ventral arm, ventral forearm, dorsal arm, dorsal forearm, antecubital fossa, trunk, lower limb, other [if other, a specification should be provided]), and if it was collected from lesional or non-lesional skin. If a biopsy was not taken, a reason should be provided.

11.7.4 Exit interview

Native English-/German-speaking subjects at selected trial sites in Canada, Germany, and US will be invited to participate in an exit interview. The purpose of the exit interview is to learn about the subject's experience of AD, the treatment, perception of change in the aspects addressed by specific PROs (including whether the changes were perceived as meaningful), wristband actigraphy (if applicable), and overall experience of participating in the trial. The exit interview will be conducted in English/German by a CRO. Participants in the exit interviews will be the first approximately 50 subjects at the selected trial sites who agree to take part in an interview.

Exit interviews will be conducted as video conferences or over the telephone at a date and time agreed with the subject between the Week 12 and Week 14 visits. Exit interviews will be scheduled to occur as soon as possible after Week 16 and at the latest 24 hours before the safety follow-up visit (Week 17).

The exit interviews will be qualitative, semi-structured interviews conducted by experienced interviewers. Each interview is expected to last approximately 60 minutes. Interviewers will use the semi-structured interview guide to drive the discussion. Interviews will be audio-recorded and transcribed to accurately capture the subject's experience. Qualitative analysis of the transcripts will be conducted using thematic analysis in Atlas.ti software. The interviewers will be trained in capturing potential AEs and will report any potential AEs to the trial site as described in Section 13.2.

11.8 End of trial

End-of-treatment form

An end-of-treatment form will be completed in the eCRF for all subjects after their last dose of IMP. For subjects who completed treatment, this will be done at the Week 16 visit. For subjects who were permanently discontinued from IMP/withdrawn from the trial, this will be done at the early termination visit.

Reporting in eCRF

It will be recorded on the end-of-treatment form in the eCRF if the subject completed treatment. It will be recorded if the reason was due to the COVID-19 pandemic. Date and time of last dose of IMP will also be recorded.

End-of-trial form

At their last visit in the trial, an end-of-trial form must be completed in the eCRF for all randomized subjects. The following data will be recorded:

- If the subject completed the trial (Section 7.3). If not, it will be recorded if the reason was due to the COVID-19 pandemic.
- Date of last contact.
- Primary reason for withdrawing from the trial (death, pregnancy, adverse event, lack of efficacy (lack of efficacy on itch, lack of efficacy on visible AD symptoms, lack of efficacy on both itch and visible AD symptoms, other [if other, a specification should be provided]), withdrawal by subject, lost to follow-up, or other [if other, a specification should be provided]). In case of withdrawal by the subject, it will be recorded if the subject withdrew consent and, if yes, the date of consent withdrawal.
- If the subject attended the (nominal) primary endpoint visit (Week 16 or 16 weeks after first dose of IMP). If not, the primary reason for not attending the visit should be provided (death, pregnancy, adverse event, lack of efficacy, withdrawal by subject, lost to follow-up, or other [if other, a specification should be provided])
- If the subject attended the safety follow-up visit (Week 17). If not, the primary reason for not attending the visit (death, pregnancy, adverse event, withdrawal by subject, lost to follow-up, safety follow-up information collected at early termination visit [see Section 10.3], or other [if other, a specification should be provided]).

11.9 Estimate of total blood volume collected

Blood samples will be collected for clinical chemistry, hematology, serology, PK, PD, and safety assessments. The maximum total volume of blood to be collected during the trial will be under 200 mL. If additional blood samples are needed, the total volume of blood collected may be more than this value. However, the maximum total volume of blood will be less than that collected during a blood donation (approximately 500 mL).

11.10 Storage of biological samples

The blood and urine samples for laboratory testing (clinical chemistry, hematology, serology, and urinalysis) will be collected to monitor and ensure subject safety during the trial and will only be stored until analysis is completed by the central laboratory.

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 CTR. Any remaining PK samples may be used for semi-quantitative metabolite identification.

PD blood samples and skin biopsies will be retained for as long as the quality of the material permits evaluation but for no longer than 12 months after completion of the CTR. If the subject provides additional consent for this, the residual material from PD blood samples and skin biopsies will be transferred to a biobank established by LEO Pharma and hosted by CCI (Germany). The residual samples will be used for future research conducted by LEO Pharma. The samples will be labelled with the trial ID, subject ID, and sample date to protect subject privacy and allow for continued blinding in future analyses. The samples will be stored in the biobank for as long as the quality of the material permits evaluation and will then be destroyed.

12 Scientific rationale for trial design and appropriateness of assessments

12.1 Scientific rationale for trial design

The overall trial design is presented in Section 7.1 and illustrated in Section 3.

The trial has been designed to explore the exposure-response relationship of LEO 152020 and evaluate the efficacy and safety of orally-administered LEO 152020 compared with placebo for up to 16 weeks of treatment in adults with moderate to severe AD (Section 6, primary objective).

Population
The target patient population consists of adults with chronic moderate to severe AD not adequately controlled with topical AD treatment (or for whom topical AD treatment is not indicated).

Therefore, the most important inclusion criterion for participation in the trial is an established diagnosis of AD, as defined by the Hanifin and Rajka 1980 criteria for AD (36) to ensure correct diagnosis and rule out differential diagnosis, and a history of AD of at least 1 year prior to baseline (inclusion criterion 4).

In addition, another prerequisite for participation in the trial is a recent (within 6 months prior to baseline) documented history of inadequate response to topical AD treatments or being a patient for whom topical treatment is medically inadvisable, to ensure that the subject is candidate for oral treatment with LEO 152020 (inclusion criterion 5). Subjects with less than 3 previous documented systemic AD treatments are also eligible to participate in the trial after appropriate washout (exclusion criterion 4).

Due to the potential important risk of CCI [redacted], exclusion criteria have been defined to exclude subjects with CCI [redacted] from participation in the trial (see Section 8.3 for the exclusion criteria and Section 5.5 for mitigation of the risk of QT prolongation).

The other eligibility criteria have been chosen to ensure inclusion of the targeted patient population, ensure subject safety, and minimize factors which could interfere with the trial assessments and procedures (Section 8.2 and Section 8.3).

Approximately 30% subjects with EASI between 7.1 and 16 at baseline (7.1≤ EASI ≤16) and 70% subjects with EASI between 16.1 and 50 at baseline (16.1≤ EASI ≤50) will be randomized in the trial to ensure a trial population representative of the target patient population.

Treatment groups

Based on PK, PD, and safety results of the first-in-human trial with LEO 152020 (39), population PK simulations, CCI analysis, and published data of other H4R compounds (28), the currently identified dosing bracket to proceed with for development of LEO 152020 is between CCI and CCI To inform phase 3 dose selection, the dose regimens LEO 152020 CCI LEO 152020 CCI and LEO 152020 CCI were therefore selected for investigation in this trial.

The treatment groups will be conducted in parallel as all selected dose regimens were demonstrated well tolerated in the first-in-human trial with LEO 152020 (39). The LEO 152020 CCI treatment group has been included to explore whether a CCI dose of LEO 152020 could be efficacious to treat AD.

The placebo treatment group will serve as control to evaluate the efficacy and safety of LEO 152020.

Trial periods

The maximum duration of the screening period was set to 5 weeks in total to ensure that the general medical condition of the subject, as established by the examinations and laboratory assessments conducted at the screening visit, has not significantly changed by baseline while allowing enough time for complete washout of any disallowed AD treatment (Section 7.1).

The 1-week run-in period is to ensure washout of any topical AD treatment and establish a baseline for AD symptoms (ADSD, Section 11.3.4) as well as nocturnal CCI and CCI data (Section 11.7.2). The subject will be asked to apply a background treatment (emollient) on lesional and non-lesional skin at least twice daily for at least 7 consecutive days to keep their skin well-moisturized and mitigate the absence of systemic and/or topical AD treatment(s).

AD is a chronic condition and based on published data of another H4R antagonist (28) the 16-week treatment duration is to ensure that LEO 152020 will reach maximum effect. During the treatment period, the subject will be asked to continue applying the emollient as needed, in complement to treatment with LEO 152020 (standard of care).

After the last dose of IMP, the 7-day safety follow-up period has a duration superior to [redacted] half-lives of LEO 152020 and is to allow complete washout of LEO 152020 before the last safety assessments are conducted.

Mitigation of bias
Triple blinding (subject, investigator, and assessor of the data/study [sponsor]) will minimize ascertainment bias (Section 9.3.2).

The combination of randomization and blinding will minimize the likelihood of allocation bias. The risk of allocation bias will further be reduced through the use of central randomization, i.e. the randomization will not be stratified by site nor will complete blocks be allocated to sites. The use of randomization will also ensure that baseline factors are not confounded with treatment. The use of a permuted block randomization within the strata defined by baseline disease severity (EASI at baseline) and region (Japan and non-Japanese countries) will limit any potential imbalance in the allocation of subjects across these factors (Section 7.1).

Endpoints and estimands
The endpoints have been selected to evaluate the efficacy of LEO 152020 in improving the severity and extent of AD, including objective signs of the disease, subjective symptoms (e.g. itch), as well as HRQoL.

Change in EASI score from baseline to Week 16 has been chosen as primary endpoint because EASI allows capturing change in disease on a continuous scale with a degree of precision making it a suitable tool for modelling the exposure-response relationship of LEO 152020 (54).

The primary estimand addressing the primary endpoint will use the hypothetical strategy to handle the occurrence of intercurrent events (initiation of rescue treatment or permanent discontinuation of IMP). The estimand addresses the clinical question, what would the effect of treatment be, if subjects adhered to the specified treatment regimen, i.e. did not permanently discontinue IMP and did not receive rescue treatment. The estimated treatment effect can be interpreted as the expected benefit of treatment if subjects adhered to the treatment regimen.

12.2 Appropriateness of assessments

All trial assessments and procedures are listed in the schedule of trial procedures (Section 4).

Efficacy assessments
EASI, vIGA-AD, and SCORAD are validated measures used in clinical practice and/or clinical trials by investigators to assess the severity and extend of AD (Sections 11.3.1 to 11.3.3). SCORAD additionally assesses subjective symptoms.

ADSD is a validated diary developed by LEO Pharma for subjects to assess the severity of 9 key signs and symptoms of AD (Section 11.3.4).

PROs
A range of validated PROs will be used to assess subject perception of AD. The PROs have been selected to cover key signs and symptoms of AD (including CCI as well as health-related quality of life (including CCI quality and impact of CCI on sleep quality), mental health, and work productivity (Sections 11.5.7 to 11.5.13). The PROs are scheduled in a combination to balance the time spent by the subject on these questionnaires at the trial site and daily in the eDiary.

Safety assessments
Standard clinical methods of subject evaluations, such as AE monitoring (Section 13), vital signs, physical examinations, ECG, laboratory testing including pregnancy testing (Section 11.4) will be used to assess subject safety.

Due to the important potential risk of CCI, subjects' ECGs will be monitored as described in Section 11.4.3 and the ECG endpoints will be used to assess effect of treatment on CCI.

An independent DMC will review all safety data and monitor the overall conduct of the trial periodically (Appendix 3H).

Pharmacokinetic assessments
Plasma concentration of LEO 152020 (C_{trough} and C_{max}) will be measured pre- and/or post-dose of IMP and PK parameters will be derived to explore the exposure-response relationship of LEO 152020 (Section 11.6).

Based on data from the first-in-human trial with LEO 152020 (39), C_{max} is expected to occur at CCI Therefore, post-dose PK blood samples will be collected shortly after the post-dose ECG measurement (see Panel 3 for more information).

Pharmacodynamics assessments
H4R is expressed on many types of immune cells including dendritic cells, mast cells, eosinophils and Th2 cells. Inhibition of H4R signaling has been demonstrated to reduce migration of immune cells to the skin site of inflammation and reduce levels of cytokines and other proinflammatory mediators in mouse skin (mouse skin inflammation models) (55-59). In humans, inhibition of H4R signaling is expected to reduce inflammation in AD lesional skin, leading to improvement of AD symptoms.

The purpose of including biomarker assessments is to investigate the effect of LEO 152020 on systemic molecular markers of AD (Section 11.6.2) and on markers of AD in skin lesions (see Section 11.7.3). Inflammatory markers (cytokines and chemokines) associated with AD (e.g. CCL17, sIL-2R, IL-13, IL-22, IgE) will be measured in serum over time to determine AD burden. Skin biopsies will be analyzed for the expression of genes involved in the pathogenesis of AD including inflammatory genes, genes involved in immune function, and genes involved in skin differentiation and barrier function. The purpose is to show disease resolution at the molecular level. In addition, transcriptome profiling of skin biopsies will be used to identify any markers or combination of markers that predict treatment response, thus allowing for a precision medicine approach, should such markers be identified.

Nocturnal CCI and sleep monitoring
Wristband actigraphy is considered relevant for evaluating the effects of treatment on nocturnal CCI and sleep CCI as motion data can be captured in a safe, non-invasive, and objective manner (Section 11.7.2).

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

AE data must be collected from time of first trial-related activity after the subject has signed the informed consent form (ICF) until subject's completion of the clinical trial (all trial periods including safety follow-up visit at Week 17, see Section 7.3).

AEs must be assessed by medically qualified personnel.

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

Any potential AE reported by the subjects during an exit interview must be collected by the interviewer on the Potential Adverse Event Collection Form. The interviewer must forward the completed form to the investigator within 24 hours of the interview. The investigator must evaluate if the potential AEs are indeed to be considered as AEs and whether they were already recorded in the eCRF and date and sign their evaluation within 24 hours of receipt of the form. Interviewer and investigator should confirm to each other receipt of the form by the investigator within those 24 hours. If the confirmed AEs were not recorded in the eCRF, or if the investigator is in doubt, they must record the AEs in the eCRF. If considered relevant, the investigator should follow up on the AEs with the subject no later than at the safety follow-up visit. If a potential AE qualifies as an SAE, the SAE must be reported within 24 hours of receipt by the site/investigator as described in Section 13.4.1.

Principles for data recording in the eCRF are described in Sections 11.4.1 to 11.4.4.

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 (e.g. 'allergic contact dermatitis').

The duration of the AE must be reported by the start date and stop date of the event unless the event is ongoing. If the event is ongoing, it will be marked as ongoing. In addition, it will be recorded if the AE started prior to first administration 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 in the eCRF (dose not changed, drug interrupted, drug withdrawn, not applicable, unknown).

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

It must be recorded in the eCRF if the AE led to permanent discontinuation of IMP and/or withdrawal from trial.

13.4 Reporting of serious adverse events

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

13.4.1 Investigator reporting responsibilities

Any SAE must be reported to LEO Pharma on the (paper) SAE form within 24 hours of first knowledge. For timing of SAE reporting in Germany, see Appendix 4. This report should contain amongst others 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. For more details regarding reporting of any SAE, please see the guidance text on the SAE form.

By signing and dating the SAE form, the investigator acknowledges that he/she is aware of the SAE and has assessed the causal relationship of the IMP(s) and any of the other medications to the SAE.

The actual reporter, if not the investigator, should also sign and date the SAE form.

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 7226 3287.

If relevant, the investigator will enclose other information with the SAE form, such as anonymized 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 should not be routinely sought or recorded. 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 an SAE is expected. The relevant reference safety information document for this clinical trial is the investigator's brochure edition 3.0 Section 7.2 and subsequent updates.

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 (33), and which are unexpected (suspected, unexpected serious adverse reactions [SUSARs]), are subject to expedited reporting to regulatory authorities, IEC(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.

In US, the following reporting requirements apply: all SAEs which are assessed as causally related to the IMP(s) by LEO Pharma (60, 61) and which are unexpected (serious and unexpected suspected adverse reactions [IND safety report]) are subject to expedited reporting to regulatory authorities, IRB(s). Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

13.5 Other events that require expedited reporting

13.5.1 Pregnancy

Any pregnancy occurring after first exposure to IMP and until the subject has completed the 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 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 and be withdrawn from the trial (Section 10.2 and Section 10.3).

13.6 Reporting of other events

13.6.1 Adverse events of special interest

The events listed in Panel 13 are considered AESIs in this trial and will require additional data to be recorded in the eCRF. LEO Pharma may request that the investigator forwards additional test results, as appropriate. An AESI may be serious or non-serious. Serious AESIs require expedited reporting via the SAE form as described in Section 13.4. AESIs will be reviewed by the DMC (Appendix 3H).

Panel 13: Adverse events of special interest

Adverse event of special interest	Rationale	Additional data to be recorded	Data collection method
Eczema herpeticum	Eczema herpeticum is a well-known severe skin infection in patients with AD which occurs in lesional skin. The additional information will be collected to better understand the pathogenic nature of the eczema.	Skin findings: • Lesion type (papules, vesicles, crusts, eroded pits, other [if other, a specification should be provided]). • Disseminated / localized. • 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 (PCR, viral culture, Tzanck test, other [if other, a specification should be provided], not confirmed).	eCRF
Skin infection requiring systemic treatment	Patients with AD are predisposed to develop skin infections due to impaired skin barrier and modified cutaneous immune response. Bacterial and viral infections represent the most common complications of AD. The additional information will be collected to better understand the pathogenic nature and localization of the skin infection.	• Location (face, scalp, back, chest, upper limb, lower limb, genitals). • Outcome of pathogenic swab (positive [staphylococcus aureus, streptococcus, candida, other, if other, a specification should be provided], negative, not performed).	eCRF

Adverse event of special interest	Rationale	Additional data to be recorded	Data collection method
Electrocardiogram CCI [redacted]	This AESI was defined based on data from the first-in-human trial with LEO 152020 (39)	• ECG (measured according to the schedule of trial procedures [Section 4]). • Severity of the CCI [redacted] (mild, moderate, severe, see QTcF severity criteria in Panel 14). • Symptoms believed to be related to the CCI [redacted] and duration of the symptoms.	eCRF

Abbreviations: AD = atopic dermatitis; AESI = adverse event of special interest; ECG = electrocardiogram; eCRF = electronic case report form; PCR = polymerase chain reaction (test); CCI [redacted]

AESIs of electrocardiogram QT corrected interval prolonged

QTcF >450 ms (men) and QTcF >460 ms (women) are considered clinically relevant QT prolongations and must be reported as AEs. QTcF severity of the AE must be recorded in the eCRF (see Panel 14 for guidance). For guidance on handling events of QT prolongation, see Section 11.4.3.

Panel 14: Severity specifications for adverse event of electrocardiogram CCI [redacted] [a]

Mild	Moderate	Severe
Men: 450 ms< average CCI [redacted] ≤480 ms Women: 460 ms< average CCI [redacted] ≤480 ms	480 ms< average CCI [redacted] ≤500 ms or 30 ms < increase in CCI [redacted] from baseline ≤60 ms	Average QTcF >500 ms or Increase in QTcF from baseline >60 ms

Abbreviations: CCI [redacted]

[a] Modified from (62) in line with the CCI [redacted] guideline on clinical evaluation of CCI [redacted] (34).

13.6.2 Medication error

Medication error refers to any unintentional error in the dispensing or administration of an IMP. Medication errors include accidental overdose or underdose, inappropriate schedule of product administration ([redacted] doses of IMP taken less than [redacted] hours apart), incorrect route of product administration, wrong product administered, expired product administered.

At each visit between Week 0 and Week 16, the investigator will ask the subject if they took any consecutive doses of IMP less than [redacted] hours apart. If this happened, the investigator will report each incidence as a medication error in the eCRF.

Reporting in eCRF
Medication errors must be recorded in the eCRF, on the AE form. For accidental overdose or underdose, only cases for which a clinical consequence occurred or could have occurred based on the investigator's judgement should be recorded in the eCRF.

In addition, any clinical consequence of the medication error must be recorded as a separate AE on the AE form. If the AE originating from the medication error qualifies as an SAE, expedited reporting will be required (Section 13.4).

13.6.3 Misuse or abuse

The terms misuse and abuse are similar in that they both represent the intentional use of a drug in a way other than defined in the CTP.

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

Abuse refers to intentional use of the IMP for what could be considered desirable non-therapeutic effects (e.g. sedative, stimulant, euphoric effects).

Misuse and abuse must be recorded on the AE form in the eCRF. In addition, any clinical consequence of misuse or abuse must be recorded as a separate AE on the AE form. If the AE originating from the misuse or abuse qualifies as an SAE, expedited reporting will be required (Section 13.4).

13.6.4 Aggravation of condition

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

As AD is a fluctuating disease, an AE should only be reported if the aggravation/exacerbation/worsening exceeds normal disease fluctuation or if lesions start appearing in a body area which is normally not affected by AD.

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). The investigator should follow up on the outcome of all non-serious AEs classified as possibly or probably related to the IMP until the safety follow-up visit or until the final outcome is determined, whichever comes first. Non-serious AEs classified as not related to the IMP do not need to be followed up for the final outcome after the subject has left the trial.

All 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 stabilized and from which the subject cannot be expected to recover during the trial or the safety follow-up periods, e.g. chronic or stabilized conditions, the final outcome at the discretion of the investigator should be reported as ‘recovering/resolving’ or ‘not recovered/not resolved’. In addition, a statement detailing why the subject cannot be expected to recover during the trial, e.g. that the SAE has stabilized 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* (63).

If the investigator becomes aware of information that requires an immediate change in a clinical trial procedure or a temporary halt of the clinical trial 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 a clinical trial procedure or of the temporary halt; the investigator will provide 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

A total of 224 subjects, including 28 Japanese subjects will be randomised in a 4:3:3:4 ratio to the following treatment groups:

- LEO 152020 CCI
- LEO 152020 CCI
- LEO 152020 CCI
- Placebo CCI

The sample size is chosen, based on the results of a simulation, to approximately provide 90% power to reject the null hypothesis that the difference in the mean change in EASI score from baseline to Week 16 between the CCI and placebo CCI groups is greater than or equal to 0. The underlying assumptions for the simulation are presented below.

To approximate the power, 1,000 data sets with 224 subjects were generated based on the specified randomization scheme in Section 7.1. Each data set was analyzed based on the main analysis of the primary estimand specified in Section 14.3.8.1. The FWER for the analysis of each simulated data set was controlled based on the procedure specified in Section 14.3.7. The simulation made separate assumptions for the EASI response trajectory and rate of intercurrent events depending on baseline disease severity. For a given level of baseline disease severity, the assumed EASI response trajectory and rate of intercurrent events for the active arms, CCI CCI and CCI are assumed to be the same.

For subjects with a baseline EASI score between CCI the assumed response trajectory, in terms of the mean change in EASI score from baseline through Week 16, and the rate of intercurrent events, used to inform the simulation, are provided in Panel 15. The correlation matrix was assumed to have an AR(1) structure, with a correlation parameter equal to 0.65 and a residual variance assumed to be 18.9.

Panel 15: Assumed response trajectories and rates of intercurrent events by treatment group, for subjects with baseline EASI score between [CCI]

	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16
Mean change from baseline to Week 16 in EASI score								
LEO 152020	CCI							
Placebo								
Proportion of subjects experiencing intercurrent event from the trial (%)								
LEO 152020	CCI							
Placebo								

Abbreviation: EASI = Eczema Area and Severity Index.

For subjects with a baseline EASI score between [CCI], data was resampled from a previous phase 3 development program in AD conducted in a similar patient population (64, 65). The observed mean change in EASI score from baseline to Week 16 and the rate of intercurrent events from the data used as the basis for resampling are provided in Panel 16.

Panel 16: Underlying response trajectories and rates of intercurrent events in the LP0162-1325 and LP0162-1326 trials for subjects with a baseline EASI score between [CCI

	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16
Mean change from baseline to Week 16 in EASI score								
LEO 152020	CCI							
Placebo								
Proportion of subjects experiencing an intercurrent event (%)								
LEO 152020	CCI							
Placebo								

Abbreviation: EASI = Eczema Area and Severity Index.

The estimated power for the treatment contrasts of interest based on the simulation are provided in Panel 17.

Panel 17: Estimated power for the treatment contrasts of interest with respect to the primary endpoint

Treatment contrast (difference in the mean change in EASI from baseline to Week 16)	Estimated marginal power	Estimated power (Hochberg) [a]
LEO 152020 CCI [redacted] vs. placebo CCI [redacted]	90.8%	90.8%
LEO 152020 CCI [redacted] vs. placebo CCI [redacted]	85.3%	79.4%
LEO 152020 CCI [redacted] vs. placebo CCI [redacted]	85.3%	79.4%

Abbreviations: EASI = Eczema Area Severity Index; FWER = familywise error rate.

[a] The Hochberg gatekeeping procedure that is to be implemented in order to control the FWER is described in Section 14.3.7.

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All subjects randomized and exposed to IMP will be included in the full analysis set and will be analyzed for efficacy based on the planned (randomized) treatment allocation. Exclusions from the full analysis set can be considered in special cases as described in ICH E9, Section 5.2.1, Full Analysis Set. If it is decided to exclude a subject from the full analysis set, a justification addressing ICH E9 will be given.

A safety analysis set will be defined as all subjects who were exposed to IMP and will be analyzed according to the actual treatment received.

A PK analysis set will be defined as all subjects who were exposed to active IMP and provided at least one sample for measuring LEO 152020 plasma concentration.

Additionally, a $FAS_{actigraphy}$ analysis set will be defined as the subset of subjects in the FAS who have signed the informed consents for the actigraphy devices.

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

14.3 Statistical analysis

14.3.1 General principles

All significance tests will be two-sided using the 5% significance level. All confidence intervals will be presented with 95% degree of confidence, unless otherwise specified. Efficacy analyses will be based on the FAS, and safety analyses will be based on the SAF.

If not mentioned otherwise, endpoints will be summarized descriptively at each relevant visit by treatment group. For endpoints evaluated over time, plots will be made to explore the trajectory with time.

An observed-cases approach will be used for tabulations of data by visit (i.e. involving only those subjects for whom data was collected at each specific visit). The number of subjects for whom data was not collected at each specific visit will also be provided.

Categorical data will be summarized by treatment group, using the number and percentage of subjects in each category. Continuous data will be summarized using the mean, median, SD, 1st quartile, 3rd quartile, minimum and maximum values. Additionally, the geometric mean and coefficient of variation (CV) will be provided for PK endpoints.

In general, for endpoints evaluated as the change from baseline and/or where a baseline adjustment is applied, baseline is defined as the assessment conducted at the randomization visit (Visit 3) if not otherwise stated.

All the analyses specified in the protocol will be reviewed in relation to the blinded data actually obtained, and the statistical analysis plan will be finalized before breaking the randomization code.

Any changes from the statistical analyses planned in this CTP will be described and justified in a protocol amendment, the statistical analysis plan and/or in the CTR, dependent on the type of change.

14.3.2 Handling of missing values

The methods for handling missing values for the primary endpoint are described in Section 14.3.8.

For other continuous endpoints for which MMRM analysis will be used, it will be assumed that missing data is missing at random. Under the MAR assumption, the estimator for a likelihood-based analysis, e.g. maximum likelihood estimation of an MMRM, is unbiased.

For dichotomized endpoints, missing data will be considered as non-response and imputed using NRI.

14.3.3 Handling of intercurrent events related to the COVID-19 pandemic

As the COVID-19 pandemic might, extraordinarily, influence trial events and data in manners not foreseen by the protocol, this section introduces statistical considerations for handling of intercurrent events related to the pandemic for the primary endpoint.

Interruption of IMP during the treatment period is not considered as an intercurrent event as LEO Pharma, in the context of a pandemic and provided local ECG monitoring is possible, will ensure continued IMP supply to the subject. Therefore, the intercurrent event, initiation of rescue medication will also be considered independent of the pandemic (see Appendix 9).

The causal relationship of permanent discontinuation of IMP related to the pandemic will be recorded in the eCRF (see also Section 10.2).

The hypothetical strategy will be used to handle the occurrence of intercurrent events related to the COVID-19 pandemic. The strategy aims to assess the effect of treatment in the hypothetical scenario, in which intercurrent events do not occur. Specifically, in the context of the pandemic, interest lies in assessing the treatment effect, if the trial were to be conducted in a setting unaffected by the COVID-19 pandemic.

The above envisioned hypothetical scenario can be formalized through the use of the potential outcome framework introduced by Rubin (66). A simplified scenario presented in Parra et al. (67), where pandemic related intercurrent events can only occur at a single timepoint will be considered. Let,

- Y represent the outcome, e.g. change in EASI from baseline to Week 16.
- A_0 represent the randomly assigned treatment.
- A_1 represent the event status for pandemic related intercurrent events.

In the potential outcome framework, it will be assumed that it is possible, through some means, to intervene on the event status for pandemic related intercurrent events. In other words, subjects can be arbitrarily assigned to experience or not experience a pandemic related intercurrent event. Based on the above specified hypothetical scenario, interest lies in the potential outcomes,

$$Y^{A_0=a_0,A_1=0}$$

which refer to the outcomes had treatment, $A_0=a_0$, been assigned and pandemic related intercurrent events were not allowed to occur. In this simplified scenario, the population level summary specified in Panel 18 can be expressed in terms of the potential outcomes as,

$$E(Y^{A_0=1,A_1=0}) - E(Y^{A_0=0,A_1=0})$$

Here, the expectations refer to the mean change in EASI score from baseline to Week 16, if all subjects had been randomized to the specified treatment group, e.g. CCI group, in a setting in which pandemic related intercurrent events do not occur ($A_1=0$). Under the consistency assumption, the observed outcome is assumed to be equal to the corresponding potential outcome. For example, the observed value for a subject randomized to treatment $A_0=1$ and who did not experience a pandemic related intercurrent event, would be equal to their potential outcome,

$$Y^{A_0=1,A_1=0}$$

For subjects experiencing a pandemic related intercurrent event, the value of the potential outcome,

$$Y^{A_0=a_0,A_1=0}$$

is not observed. In order to completely specify the hypothetical scenario of interest, one must specify how the values of the unobserved potential outcomes, i.e. the outcomes that would be observed had subjects not experienced pandemic related intercurrent events, relate to the observed data. From a missing data standpoint, this can be achieved through explicit assumptions, such as MAR or through the specification of a plausible imputation model.

If, under the hypothetical scenario, subjects are at risk for additional intercurrent events, e.g. non-pandemic related intercurrent events, imputation-based inference may need to account for the likelihood of subjects experiencing such events and subsequently handle their occurrence accordingly.

In Section 14.3.8.1, the hypothetical strategy will be used to handle the occurrence of all intercurrent events, regardless of the relation to the pandemic. In this section, the potential outcomes of interest are with respect to the outcomes that would be observed if all intercurrent events were not allowed to occur.

These assumptions will be described in general terms in Section 14.3.8 and elucidated upon in the SAP.

Handling of data affected by the COVID-19 pandemic
As a consequence of the pandemic and associated local preventive measures, subjects may miss an entire visit. At scheduled visits, it will be recorded in the eCRF whether data are missing due to the pandemic.

It should be noted that a subject may have missing data related to the pandemic, even though the subject has not experienced an intercurrent event related to the pandemic.

An overview of how observed and missing data will be handled according to the intercurrent events and their relatedness to the pandemic is presented in Panel 19 for the main analysis of each estimand. Details of the analyses are described in Section 14.3.8.

14.3.4 Disposition of subjects

The reasons for permanent discontinuation of IMP or withdrawal from trial will be presented for all randomized subjects by last visit attended and by treatment group.

A subject disposition summary table will be made including information on the number of subjects screened, randomized, exposed, completed trial, permanently discontinued IMP, and withdrawn from the trial by treatment group and overall.

14.3.5 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomized subjects and by treatment group. Presentations of age, sex, ethnicity, race, and baseline EASI score by treatment group will also be given by region and baseline disease severity (EASI score at baseline ≤16 and ≥16.1).

Other baseline characteristics include height, weight, body mass index, duration of AD, concurrent diagnoses (from medical history), concomitant medication (including indication), and previous AD treatments.

14.3.6 Exposure and treatment compliance

The duration of exposure to treatment in a specific week interval will be calculated as the number of days from date of first dose of IMP in that period to the date of last dose of IMP in that period, both days included.

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

The average number of weekly doses of IMP and the average total number of doses of IMP administered will be presented for the SAF by treatment group for week of treatment intervals and for the whole treatment period, respectively.

Treatment compliance will be presented for the SAF for each treatment group as the percentage of missed doses of IMP.

14.3.7 Testing strategy

This is a phase 2 trial with the primary objective to explore the exposure-response relationship of LEO 152020 and evaluate efficacy of LEO 152020 compared with placebo. The investigation of exposure-response relationship is regarded as an exploratory analysis supporting the understanding of the dependency from exposure on efficacy achieved. A gatekeeping procedure will be applied to control the overall type 1 error rate in the strong sense.

The gatekeeping procedure will first test the null hypothesis comparing the mean change in EASI score from baseline to Week 16 between the LEO 152020 CCI [redacted] and placebo CCI [redacted] groups. If this null hypothesis is rejected, the procedure will go on to test the null hypotheses associated with the following treatment contrasts:

- Change in EASI from baseline to Week 16 between LEO 152020 CCI [redacted] and placebo CCI [redacted]
- Change in EASI from baseline to Week 16 between LEO 152020 CCI [redacted] and placebo CCI [redacted]

Otherwise testing will stop. When testing the remaining 2 hypotheses, the Hochberg procedure will be used to control the overall type I error rate in the strong sense. The Hochberg procedure is a step-up procedure that first assesses whether the maximum of the 2 p-values is less than 0.05. If so, both hypotheses are rejected. If the maximum p-value is greater than 0.05, the procedure will move on to test the hypothesis associated with the minimum p-value at the 2.5% significance level. If the minimum p-value is less than 0.025, then the corresponding hypothesis is rejected. Hypothesis testing will be based on the main analysis of the primary estimand.

14.3.8 Analysis of primary endpoint

The primary endpoint will be analyzed differently to address the 2 aspects of the primary objective: efficacy evaluation and exploration of the exposure-response relationship.

The primary analysis will evaluate the efficacy of LEO 152020 compared with placebo. A primary and 2 supplementary estimands have been specified in order to address clinical questions of interest.

Panel 18: Primary and supplementary estimands for primary endpoint

Objective	Estimands					Endpoint
	Estimand type (Primary/ supplementary)	**Interpretation of the estimand**	**Comparison groups**	**Intercurrent events (strategy)**	**Population level summary**	
Primary objective To evaluate efficacy of LEO 152020 compared with placebo for up to 16 weeks of treatment in subjects with moderate to severe AD	Primary	Assesses the effect of treatment if subjects adhered to the treatment regimen, i.e. they did not permanently discontinue IMP and did not initiate the use of rescue medication prior to Week 16 (Section 14.3.8.1). Under this hypothetical scenario, the occurrence of IEs is assumed not to affect the change in EASI score from baseline to Week 16, i.e. the potential outcomes for subjects experiencing IEs are assumed to follow the same distribution as the outcomes for subjects in the same treatment group, who did not experience IEs.	Dose regimens of LEO 152020 CCI CCI CCI vs. placebo CCI	Permanent discontinuation of IMP due to pandemic related factors (hypothetical) Permanent discontinuation of IMP due to non-pandemic related factors (hypothetical) Initiation of rescue medication (hypothetical)	Difference in mean change in EASI from baseline to Week 16	**Primary endpoint** Change in EASI from baseline to Week 16

Objective	Estimands					Endpoint
	Estimand type (Primary/ supplementary)	**Interpretation of the estimand**	**Comparison groups**	**Intercurrent events (strategy)**	**Population level summary**	
	First supplementary	Assesses the effect of treatment in the hypothetical scenario in which the COVID-19 pandemic did not occur, regardless of the occurrence of non-pandemic related IEs (Section 14.3.8.2). Under this hypothetical scenario, the potential outcomes for subjects experiencing a pandemic related IE are assumed to follow the distribution describing the outcomes for subjects in the same treatment group who did not experience a pandemic related intercurrent event and ignoring the occurrence of non-pandemic intercurrent events.	Dose regimens of LEO 152020 CCI CCI CCI vs. placebo CCI	Permanent discontinuation of IMP due to pandemic related factors (hypothetical) Permanent discontinuation of IMP due to non-pandemic related factors (treatment policy) Initiation of rescue medication (treatment policy)	Difference in mean change in EASI from baseline to Week 16	**Primary endpoint** Change in EASI from baseline to Week 16

Objective	Estimands					Endpoint
	Estimand type (Primary/ supplementary)	**Interpretation of the estimand**	**Comparison groups**	**Intercurrent events (strategy)**	**Population level summary**	
	Second supplementary	Assesses the effect of treatment in the hypothetical scenario, in which the COVID-19 pandemic did not occur and where the occurrence of non-pandemic related IEs indicates subsequent non-response (Section 14.3.8.3). Under this hypothetical scenario, the potential outcomes for subjects experiencing a pandemic related intercurrent event are assumed to follow the distribution describing the outcomes for subjects in the same treatment group who did not experience a pandemic related intercurrent event.	Dose regimens of LEO 152020 CCI CCI CCI vs. placebo CCI	Permanent discontinuation of IMP due to pandemic related factors (hypothetical) Permanent discontinuation of IMP due to non-pandemic related factors (composite) Initiation of rescue medication (composite)	Difference in mean change in EASI from baseline to Week 16	**Primary endpoint** Change in EASI from baseline to Week 16

Abbreviations: AD = atopic dermatitis; ; COVID-19 = corona virus disease 2019; EASI = Eczema Area and Severity Index; IE = intercurrent events; IMP = investigational medicinal product.

For the evaluation of efficacy, the following intercurrent events are considered to affect the interpretation of the measurements of the endpoint/variable:

Non-pandemic related intercurrent events

- **Initiation of rescue treatment**: This event occurs when a subject initiates rescue treatment. This event can occur at the discretion of the investigator. The timing of the event is defined as the date of initiation of the rescue treatment recorded in the eCRF and the event will be handled without assessing relatedness to the COVID-19 pandemic.
- **Permanent discontinuation of IMP independently of the COVID-19 pandemic**: This event occurs when a subject permanently discontinues IMP independently of the pandemic. This event can occur at the subject's own initiative, or at the discretion of the investigator or the sponsor. The timing of the event is defined as the date of permanent discontinuation of IMP recorded in the eCRF.

Pandemic related intercurrent events

- **Permanent discontinuation of IMP due to the COVID-19 pandemic**: This event occurs when a subject permanently discontinues IMP due to circumstances related to the pandemic and is not attributed to lack of efficacy or randomized treatment features considered unacceptable by the subject.

Depending on the estimand strategy selected, the occurrence of an intercurrent event may be ignored, lead to the exclusion of data observed after the occurrence of the event, be accounted for in the definition of a composite endpoint, or restrict the relevant observation window to the time prior to the occurrence of the intercurrent event, as described below.

14.3.8.1 Primary estimand

The primary estimand will use the *hypothetical strategy* to handle the occurrence of intercurrent events. The estimand attempts to quantify the effect of treatment, in the hypothetical scenario, where subjects do not permanently discontinue IMP for any reason and where rescue medication is not made available prior to Week 16.

For subjects observed to experience an intercurrent event, the potential outcomes under the envisioned hypothetical scenario, are assumed to follow the outcome distribution for subjects in the same treatment group, who did not experience an intercurrent event.

The primary estimand assesses the expected benefit of the treatment when adhering to the treatment regimen in the context of the specified hypothetical scenario.

Main analysis
Data collected after permanent discontinuation of IMP, regardless of reason, or the initiation of rescue treatment will be excluded from the analysis and "treated as missing".

The endpoint will be analyzed using a MMRM. The model will include treatment, visit, visit by treatment interactions, and region (Japan, non-Japanese countries) as factors and be adjusted for the baseline EASI score as a covariate. The covariance matrix will be assumed to have an unstructured form and the Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Missing data, including data excluded due to the occurrence of an intercurrent event, is assumed to be MAR. The estimated LS-mean treatment differences, based on the observed margins, will be presented with 95% CIs and nominal p-values at each visit. The primary comparison is the treatment difference at Week 16, between the CCI [redacted] and placebo groups.

Sensitivity analysis
The following sensitivity analyses will assess the robustness of the results of the main analysis with respect to the underlying statistical assumptions. The impact of the missing data assumptions on data excluded after the occurrence of an intercurrent event/due to the pandemic will not be considered in the sensitivity analyses, as the MAR assumption is aligned with the envisioned hypothetical scenario.

- Sensitivity analysis 1: Exclusion of subjects with monotone missing data at Week 1
  Subjects with monotone missing data from Week 1 onwards are automatically excluded from the analysis. Although under the MAR assumption, the estimator of the treatment effect based on a likelihood analysis of a MMRM is unbiased, such exclusions run contrary to the intent of the FAS.
  This sensitivity analysis will assess the robustness of the results of the main analysis with regards to the exclusion of subjects with no observed post-baseline EASI assessments. The analysis will include all randomized subjects regardless of whether a subject has observed post-baseline EASI score assessments. To assess the impact of excluding subjects with no post-baseline EASI score assessments from the analysis, the LS-mean treatment contrasts for the MMRM specified in the main analysis, will be estimated using the mean baseline EASI score and the proportion of subjects from each region based on the FAS.

- Sensitivity analysis 2: Functional form of the baseline EASI score covariate
  This sensitivity analysis will assess the robustness of the results of the main analysis with respect to the assumed linear relationship between the mean change in EASI score from baseline to Weeks 1-16 and the baseline EASI score. Additional details for each sensitivity analysis will be specified in the SAP.

14.3.8.2 First supplementary estimand

The first supplementary estimand will use a combination of the *treatment policy and hypothetical strategies*, to handle the occurrence of non-pandemic and pandemic related intercurrent events, respectively. The treatment policy strategy attempts to quantify the effect of the decision to treat subjects with the randomized treatment and therefore ignores the occurrence of non-pandemic related intercurrent events.

This supplementary estimand will evaluate the treatment difference in the change in EASI score from baseline to Week 16 in the hypothetical scenario in which the COVID-19 pandemic did not occur and regardless of the occurrence of non-pandemic related intercurrent events. Under this hypothetical scenario, the potential outcomes for subjects experiencing a pandemic related intercurrent event are assumed to follow the observed outcome distribution, irrespective of the occurrence of non-pandemic related intercurrent events, among subjects in the same treatment group.

Main analysis
Data collected after the occurrence of a non-pandemic related intercurrent event will be included in the analysis. Whereas data collected after a pandemic related intercurrent event will be excluded from the analysis and 'treated as missing'.

Intermittent missing data will be imputed based on a Markov Chain Monte Carlo method, in order to obtain 1,000 copies of the data set with a monotone missing data pattern. Missing data, including data 'treated as missing' after the occurrence of a pandemic related intercurrent event, will be imputed assuming the data is MAR within each treatment group. For a given treatment group, the imputation model will be based on all data observed prior to the occurrence of pandemic related intercurrent events. In particular, data observed after the occurrence of non-pandemic related intercurrent events will be included in the imputation model, in line with the specified treatment policy approach for handling non-pandemic related intercurrent events.

For each of the 1,000 complete datasets, the change in EASI score from baseline to Week 16 will be analyzed using an ANCOVA model including treatment, and region (Japan, non-Japanese countries) as factors, and baseline EASI score as a covariate. The pooled estimates of the difference in the LS-mean change from baseline to Week 16, based on the observed margins, along with the associated 95% CIs and nominal p-values will be presented. Pooled inference will be based on applying Rubin's rules to the estimates and standard errors from the ANCOVA analysis of the imputed datasets.

Sensitivity analysis
A tipping point analysis will be performed based on implementing a delta-adjusted multiple imputation approach. The delta-adjusted imputation approach allows for missing data to be imputed under the MNAR assumption. Heuristically, the imputation strategy, adjusts/shifts the parameters of the MAR distribution based on the value of a numeric offset term, denoted by delta. The tipping point analysis will adjust the values of the parameters in the MAR distribution representing the mean change in EASI score from baseline to Weeks 1-16. The analysis will assess how robust the results of the main analysis are to varying departures from the MAR assumption within each active treatment group.

14.3.8.3 Second supplementary estimand

A second supplementary estimand will use a combination of the *composite* and *hypothetical strategies* to handle the occurrence of non-pandemic and pandemic related intercurrent events, respectively. In the context of this trial, the composite strategy attempts to quantify the effect of treatment, assuming that the occurrence of a non-pandemic related intercurrent event is indicative of subsequent treatment failure. For the primary endpoint, treatment failure will be defined as failing to obtain a decrease in EASI of at least 50% from baseline to Week 16.

This supplementary estimand evaluates the treatment difference in the change in EASI score from baseline to Week 16 in the hypothetical scenario in which the COVID-19 pandemic did not occur and assuming that the occurrence of non-pandemic related intercurrent events is indicative of subsequent treatment failure.

Main analysis
Data observed after the occurrence of an intercurrent event will be excluded from the analysis and "treated as missing". Intermittent missing data will be imputed using a Markov Chain Monte Carlo method, in order to obtain 1,000 copies of the data set with a monotone missing data pattern.

Monotone missing data that is not due to the pandemic and data "treated as missing" due to the occurrence of a non-pandemic related intercurrent event will be imputed under the MAR assumption, with the additional stipulation that the imputation model will be truncated in order to align with the assumption that

$$Y_{EASI,Week\ 16} > \frac{Y_{EASI,Baseline}}{2}.$$

The additional stipulation ensures that these subjects will be considered as non-responders based on the imputed Week 16 EASI score.

For subjects experiencing a pandemic related intercurrent event or with monotone missing data due to the pandemic, the imputation model needs to account for the possibility of experiencing a subsequent non-pandemic related intercurrent under the envisioned hypothetical scenario. Missing data will therefore be imputed from the joint distribution describing the time to experiencing a non-pandemic related intercurrent event and the longitudinal EASI score assessments under a MAR assumption. If the imputed time to first non-pandemic related intercurrent event is less than 16 weeks, all subsequent EASI scores for that subject will be imputed based on the above imputation model for non-pandemic related intercurrent events.

For each of the 1,000 complete datasets, the change in EASI score from baseline to Week 16 will be analyzed using an ANCOVA model including treatment and region (Japan, non-Japanese countries) as factors, and baseline EASI score as a covariate. The pooled estimates of the difference in the LS-mean change in EASI score from baseline to Week 16, based on the observed margins, along with the associated 95% CIs and nominal p-values will be presented. Pooled inference will be based on applying Rubin’s rules to the estimates and standard errors from the ANCOVA analysis of the imputed datasets.

Panel 19 presents an overview of how observed and missing data will be handled according to the intercurrent events for the analyses of estimands.

Panel 19: Handling of intercurrent events and analyses of estimands for the primary endpoint

Events	Data observed or missing	Estimand strategy		
		Primary estimand	**First supplementary estimand**	**Second supplementary estimand**
Initiation of rescue treatment [a]	Observed	Treated as missing/Not used	Used	Treated as missing, MI (MAR ensuring NR)
	Missing	Not used	MI (MAR)	MI (MAR ensuring NR)
Permanent discontinuation of IMP **independently of** the COVID-19 pandemic	Observed	Treated as missing/Not used	Used	Treated as missing, MI (MAR ensuring NR)
	Missing	Not used	MI (MAR)	MI (MAR ensuring NR)
Permanent discontinuation of IMP **due to** the COVID-19 pandemic	Observed	Treated as missing/Not used	Treated as missing, MI (MAR)	Treated as missing, MI (JM/MAR ensuring NR)
	Missing	Not used	MI (MAR)	MI (JM/MAR ensuring NR)
No intercurrent events	Observed	Used	Used	Used
	Missing **independently of** the COVID-19 pandemic	Not used	MI (MAR)	MI (MAR ensuring NR)
	Missing **due to** the COVID-19 pandemic	Not used	MI (MAR)	MI (JM/MAR ensuring NR)

Abbreviations: COVID-19 = coronavirus disease 2019; IMP = investigational medicinal product; JM = joint model; MAR = missing at random; MI = multiple imputation; NR = non-response.

[a] Initiation of rescue treatment is considered an intercurrent event regardless of the relatedness to the COVID-19 pandemic.

14.3.8.4 Exposure-response modeling of LEO 152020

To explore the exposure-response relationship of LEO 152020, the change in EASI score from baseline to Week 16 will be assessed based on an ANCOVA model, including the C_{trough} values at Week 16 and the baseline EASI score as covariates and region (Japan, non-Japanese countries) as a factor. Data observed after the occurrence of an intercurrent event, will be excluded from the analysis and "treated as missing". Week 16 data, that is either missing or "treated as missing" due to the occurrence of an intercurrent event, will be assumed to be missing at random. The difference in the LS-mean change in EASI score from baseline to Week 16, based on the observed margins, along with the associated 95% CIs and nominal p-values will be presented. In case a linear relationship between change in EASI from baseline to Week 16 and C_{trough} cannot be shown, alternative models such as non-sigmoidal (with a hill coefficient =1) E_{max} or sigmoidal E_{max} will be considered. Further details regarding the goodness of fit criteria and the non-linear model will be described in the SAP.

14.3.9 Analysis of secondary endpoints

Analysis of secondary endpoints

- Number of AEs from baseline to Week 16+3 days per subject.

is described in detail in Section 14.3.14.1.

14.3.10 Analysis of exploratory endpoints

Continuous endpoints

- EASI at each visit from Week 1 to Week 16.
- SCORAD at each visit from Week 1 to Week 16.
- Change in ADSD score (weekly average) from baseline to Week 16.
- Change in each ADSD individual symptom score (weekly average) from baseline to Week 16.

will be summarized descriptively at each visit by treatment group and will be analyzed using an MMRM. The model will include treatment, visit, visit by treatment interaction terms, region (Japan, non-Japanese countries), and baseline disease severity (EASI score at baseline ≤16 and ≥16.1) as factors and adjust for the baseline value of the endpoint of interest as a covariate. For the analysis of the EASI score at each visit, the baseline disease severity factor will be excluded from the MMRM in order to avoid introducing a discontinuity in the relationship between the post-baseline EASI scores and the baseline EASI score. The model

will use an unstructured covariance matrix, and the Kenward-Roger approximation to estimate the denominator degrees of freedom. The SAP will specify alternative structures for the covariance matrix, to be used in case of non-convergence. For these endpoints, data collected after permanent discontinuation of IMP or after initiation of rescue medication will be excluded from the analysis and 'treated as missing'. Missing data will be assumed to be MAR. The estimates will be presented with 95% CIs and nominal p-values at each visit.

Binary endpoints

- Having a decrease in EASI of at least 50% (EASI 50) from baseline to Week 16.
- Having a decrease in EASI of at least 75% (EASI 75) from baseline to Week 16.
- Having a decrease in EASI of at least 90% (EASI 90) from baseline to Week 16.
- Having vIGA-AD of 0 (clear) or 1 (almost clear) at Week 16.
- Having a decrease in vIGA-AD of at least 2 points from baseline to Week 16.
- Having a decrease in ADSD CCI score (weekly average) of at least 4 points from baseline to Week 16 in subjects with ADSD CCI score ≥4 at baseline.

will be summarized descriptively at each visit by treatment group and will be analyzed based on a logistic regression model, including region (Japan, non-Japanese countries) and baseline disease severity (EASI score at baseline ≤16 and ≥16.1) as factors and adjusting for the baseline value of the endpoint as a covariate. The logistic regression model will be used to estimate the risk difference and associated 95% confidence interval based on the standardized estimator presented in Ge et al. (68). For the analysis of the EASI responder endpoints, baseline disease severity will not be included as a factor in the logistic regression model. Subjects who prior to the Week 16 visit received rescue treatment or permanently discontinued IMP or have missing data will be considered as non-responders.

Time-to-event endpoint

- Time from randomization to having an observed decrease in EASI of at least 50% (EASI 50) from baseline.
- Time from randomization to having a decrease in ADSD CCI score (weekly average) of at least 4 points from baseline in subjects with ADSD CCI score ≥ 4 at baseline.

will be analyzed according to Gray's test, stratified by region (Japan, non-Japanese countries) and baseline disease severity (EASI score at baseline ≤16 and ≥16.1). Gray's test accounts for the occurrence of the competing risks, permanent discontinuation of IMP and initiation of

rescue medication. Inference will be based on the estimated cumulative incidence functions derived from the Aalen-Johansen estimator. The estimated cumulative incidence functions will be presented by treatment group along with pointwise 95% confidence intervals. In addition, the estimated sub-distributional hazard ratio from a Fine and Gray model, stratified by region (Japan, non-Japanese countries) and baseline disease severity (EASI score at baseline ≤16 and ≥16.1) and adjusted for the baseline value of the endpoint of interest, will be presented along with the corresponding 95% CI.

The following sleep CCI and nocturnal CCI endpoints will be collected using actigraphy:

- Change in CCI from baseline to Week 16. The endpoint is measured in minutes and weekly averages will be reported.
- Change in number of nocturnal CCI events per hour from baseline to Week 16. The endpoint will be assessed daily and the weekly averages will be reported.
- Change in duration of nocturnal CCI events per hour from baseline to Week 16. The endpoint will be assessed daily and the weekly averages will be reported.
- Change in CCI from baseline to Week CCI CCI is calculated as the proportion of time spent CCI versus total time CCI, expressed as a percentage. This will be assessed daily and weekly averages will be reported.

These endpoints will be summarized descriptively by week and treatment group. The weekly average of data collected using actigraphy will be based on data collected over 7 days. Data collected after the initiation of rescue medication or permanent discontinuation of IMP will be excluded from the calculation of the weekly averages. In order to calculate the weekly average, a minimum of 4 out of the 7 planned measurements will be required.

The following sleep disturbance endpoints will be collected using the eDiary and summarized descriptively by week and treatment group:

- Difficulty CCI at Week CCI
- Frequency of CCI During the Night at Week CCI
- CCI at Week CCI
- CCI at Week CCI

14.3.11 Analysis of patient-reported outcomes

Continuous endpoints

- Change in POEM from baseline to Week 16.
- Change in DLQI from baseline to Week 16.
- Change in EQ-5D-5L from baseline to Week 16.

will be summarized descriptively by week and treatment group and will be analyzed using the same MMRM model described in Section 14.3.10 for continuous endpoints.

The following endpoints

- Change in HADS from baseline to Week 16.
- Change in WPAI:AD (for each individual domain) from baseline to Week 16.

will be analyzed using an ANCOVA model including treatment, region (Japan, non-Japanese countries), and baseline disease severity (EASI score at baseline ≤16 and ≥16.1) as factors and adjusted for the baseline score as covariate. Data collected after the occurrence of an intercurrent event will be excluded from the analysis and "treated as missing". Missing data will be assumed to be MAR.

Binary endpoints

- Having a decrease in DLQI of at least 4 points from baseline to Week 16 in subjects with DLQI ≥4 at baseline.
- Having a decrease in POEM of at least 4 points from baseline at Week 16 in subjects with POEM≥4 at baseline.

will be summarized descriptively at each visit by treatment group and will be analyzed using the same logistic regression model described in Section 14.3.10 for binary endpoints.

14.3.12 Analysis of pharmacodynamics

Exploratory analyses for the following endpoints will be conducted for the total population as well as by baseline disease severity (EASI score at baseline ≤16 and ≥16.1)

- Change in expression levels of blood biomarkers from baseline to Week CCI
- Change in expression levels of AD disease biomarkers in skin from baseline to Week CCI

The biomarker results will be reported in an addendum to the CTR. If biopsies are collected from less than 10% of the randomized subjects in a specific treatment group, analysis may not be carried out for that treatment group as the number of biopsies may be too low to allow for a meaningful analysis.

14.3.13 Exploratory analyses

Additional exploratory analyses will be described in the SAP and will be conducted if deemed necessary.

14.3.14 Analysis of safety

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

14.3.14.1 Adverse events

AEs will be coded during the trial according to MedDRA. AEs will be presented by preferred term and primary SOC.

Treatment-emergent AEs will be summarized; however, all AEs recorded during the trial will be included in subject data listings. Treatment-emergent and non-treatment-emergent AEs will be listed separately. An event will be considered treatment-emergent if started after the first dose of IMP or if started before the first dose of IMP and worsened in severity after first dose of IMP. An event will not be considered treatment-emergent if started 3 days after the last dose of IMP. The tabulations described below will only include the treatment-emergent AEs. In each of the tabulations, AEs are defined by MedDRA preferred terms within primary SOC.

AEs will be summarized in terms of the number of subjects with at least 1 event, the percentage of subjects with at least 1 event, the number of events, and the event rate per 100 patient years of observation time.

Related AEs are defined as AEs for which the investigator has not described the causal relationship to IMP as ‘not related’.

An overall summary of the number of events and the number (percentage) of subjects with any treatment-emergent AEs, deaths, SAEs, AESIs, permanent discontinuations from IMP and/or withdrawals from the trial due to AEs, treatment-related AEs, mild and moderate AEs and severe AEs will be presented.

Tabulations by SOC and preferred term will be presented by treatment group for all AEs, SAEs, related AEs, AESIs, and AEs leading to permanent discontinuation of IMP and/or withdrawal from trial. In addition, all AEs will be presented by severity and causal relationship to IMP, respectively.

The number of AEs and number of subjects with each type of AE (as described in the paragraph above) will be tabulated by treatment group from baseline to Week 16+3 days.

SAEs will be evaluated separately and a narrative will be given.

AESIs will be tabulated and listed by treatment group, no narratives will be given except if these are serious.

AEs leading to withdrawal from trial and/or permanent discontinuation of IMP will be tabulated and listed. The detailed listing will provide an overview of the individual cases and include the age and sex of the subject, treatment received at the time of AE onset, the AE preferred and reported terms, causality and severity of the AE, the action taken with the IMP, AE outcome, start and stop date of AE, duration of AE, and number of days since first and last administration of IMP. No narratives will be given.

14.3.14.2 Vital signs and physical examination

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

Subjects with abnormal, clinically significant physical findings will be listed. Furthermore, a shift table for physical findings showing the change from baseline to Week 16 in clinical assessments (normal; abnormal, not clinically significant; abnormal, clinically significant) will be performed.

14.3.14.3 Electrocardiography

Absolute values and change in ECG parameters (CCI) from baseline to each relevant visit will be summarized by treatment group as mean, SD, median, minimum and maximum values for the safety analysis set.

Subjects with abnormal clinically significant ECG parameters will be listed. Furthermore, a shift table showing the change in clinical assessments (normal, abnormal not clinically significant, abnormal clinically significant) for the ECG parameters from baseline to Week 16 will be provided.

14.3.14.4 Clinical laboratory evaluation

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

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

14.3.15 Pharmacokinetic analysis

The PK endpoint

- C_{trough} of LEO 152020 at Weeks CCI
- C_{max} of LEO 152020 at Weeks CCI .

will be summarized for subjects in the PK analysis set and with PK assessments at the relevant visits using geometric mean, coefficient of variation (derived based on a log-normal distribution assumption), median, 1st quartile, 3rd quartile, minimum and maximum values.

14.3.16 Interim analysis

No interim analysis is planned.

15 References

1. Leung DY, Bieber T. Atopic dermatitis. Lancet. 2003;36(9352):151-160.

2. Abramovits W. Atopic dermatitis. J Am Acad Dermatol. 2005;53(1 Suppl 1):S86-93.

3. Fishbein AB, Silverberg JI, Wilson EJ, Ong PY. Update on Atopic Dermatitis: Diagnosis, Severity Assessment, and Treatment Selection. J Allergy Clin Immunol Pract. 2020;8(1):91-101.

4. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. PLoS One. 2012;7(7):e39803.

5. Abuabara K, Yu AM, Okhovat JP, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: A systematic review and meta-analysis of longitudinal studies. Allergy. 2018;73(3):696-704.

6. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol. 2013;132(5):1132-1138.

7. Gittler JK, Shemer A, Suárez-Fariñas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQF, Mitsui H, Cardinale I, de Guzman Strong C, Krueger JG, Guttman-Yassky E. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. The Journal of allergy and clinical immunology. 2012;130(6):1344-1354.

8. De Benedetto A, Kubo A, Beck LA. Skin barrier disruption: a requirement for allergen sensitization? J Invest Dermatol. 2012;132(3 Pt 2):949-963.

9. Davidson S, Giesler GJ. The multiple pathways for itch and their interactions with pain. Trends Neurosci. 2010;33(12):550-558.

10. Silverberg JI, Pinter A, Pulka G, Poulin Y, Bouaziz J-D, Wollenberg A, Murrell DF, Alexis A, Lindsey L, Ahmad F, et al. Phase 2B randomized study of nemolizumab in

adults with moderate-to-severe atopic dermatitis and severe pruritus. Journal of Allergy and Clinical Immunology. 2020;145(1):173-182.

11. Buddenkotte J, Steinhoff M. Pathophysiology and therapy of pruritus in allergic and atopic diseases. Allergy. 2010;65(7):805-821.

12. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-2223.

13. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2163-2196.

14. Jeon C, Yan D, Nakamura M, Sekhon S, Bhutani T, Berger T, Liao W. Frequency and Management of Sleep Disturbance in Adults with Atopic Dermatitis: A Systematic Review. Dermatol Ther (Heidelb). 2017;7(3):349-364.

15. Yu SH, Attarian H, Zee P, Silverberg JI. Burden of Sleep and Fatigue in US Adults With Atopic Dermatitis. Dermatitis. 2016;27(2):50-58.

16. Tollefson MM, Bruckner AL. Atopic dermatitis: skin-directed management. Pediatrics. 2014;134(6):e1735-1744.

17. Watson W, Kapur S. Atopic dermatitis. Allergy Asthma Clin Immunol. 2011;7 Suppl 1(Suppl 1):S4.

18. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, Gieler U, Lipozencic J, Luger T, Oranje AP, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. J Eur Acad Dermatol Venereol. 2012;26(9):1176-1193.

19. Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, Bergman JN, Chamlin SL, Cohen DE, Cooper KD, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014;71(1):116-132.

20. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, Chamlin SL, Cooper KD, Feldman SR, Hanifin JM, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71(2):327-349.

21. Gutzmer R, Gschwandtner M, Rossbach K, Mommert S, Werfel T, Kietzmann M, Baeumer W. Pathogenetic and therapeutic implications of the histamine H4 receptor in inflammatory skin diseases and pruritus. Front Biosci (Schol Ed). 2011;3:985-994.

22. De Benedetto A, Yoshida T, Fridy S, Park JE, Kuo IH, Beck LA. Histamine and Skin Barrier: Are Histamine Antagonists Useful for the Prevention or Treatment of Atopic Dermatitis? J Clin Med. 2015;4(4):741-755.

23. Matterne U, Böhmer MM, Weisshaar E, Jupiter A, Carter B, Apfelbacher CJ. Oral H1 antihistamines as 'add-on' therapy to topical treatment for eczema. Cochrane Database Syst Rev. 2019;1(1):Cd012167.

24. Thurmond RL. The histamine H4 receptor: from orphan to the clinic. Front Pharmacol. 2015;6:65.

25. Ko K, Kim HJ, Ho PS, Lee SO, Lee JE, Min CR, Kim YC, Yoon JH, Park EJ, Kwon YJ, et al. Discovery of a Novel Highly Selective Histamine H4 Receptor Antagonist for the Treatment of Atopic Dermatitis. J Med Chem. 2018;61(7):2949-2961.

26. Schaper-Gerhardt K, Rossbach K, Nikolouli E, Werfel T, Gutzmer R, Mommert S. The role of the histamine H(4) receptor in atopic dermatitis and psoriasis. Br J Pharmacol. 2020;177(3):490-502.

27. Mehta P, Miszta P, Rzodkiewicz P, Michalak O, Krzeczyński P, Filipek S. Enigmatic Histamine Receptor H(4) for Potential Treatment of Multiple Inflammatory, Autoimmune, and Related Diseases. Life (Basel). 2020;10(4).

28. Werfel T, Layton G, Yeadon M, Whitlock L, Osterloh I, Jimenez P, Liu W, Lynch V, Asher A, Tsianakas A, Purkins L. Efficacy and safety of the histamine H(4) receptor antagonist ZPL-3893787 in patients with atopic dermatitis. J Allergy Clin Immunol. 2019;143(5):1830-1837.e1834.

29. Murata Y, Song M, Kikuchi H, Hisamichi K, Xu XL, Greenspan A, Kato M, Chiou CF, Kato T, Guzzo C, et al. Phase 2a, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of a H4 R-antagonist (JNJ-39758979) in Japanese adults with moderate atopic dermatitis. J Dermatol. 2015;42(2):129-139.

30. LEO Pharma. LEO 152020 Investigator's Brochure Edition 3.0. 2020.

31. ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Clinical and Non-Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential Q&As. (E14)(S7B), Step 1; 15-Nov. 2018.

32. WMA: World Medical Association. Declaration of Helsinki – ethical principles for medical research involving human subjects. Amended by the 64th WMA General Assembly, Fortaleza, Brazil. 2013.

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

34. ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: CCI [redacted] Step 4; 12-May. 2005.

35. EMA: European Medicines Agency. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic. Version 3. 2020.

36. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. 1980;60(92):44-47.

37. FDA. Food and Drug Administration. Draft Guidance for Industry. Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing. 2020.

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

39. Park M: Single and Multiple Ascending Dose Study of JW1601 for Healthy Volunteers. In *ClinicalTrialsgov NCT04018170*. JW Pharmaceutical; 2020.

40. European Commission. EudraLex: The Rules Governing Medicinal Products in the European Union. Guidelines for good manufacturing practices for medicinal products for human and veterinary use. 2010;Volume 4.

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

42. HOME. Harmonising Outcome Measures for Eczema. Eczema Area and Severity Index (EASI) case report form. Aged 8 and over. 2017.

43. Eli Lilly and Company: Validated Investigator Global Assessment scale for Atopic Dermatitis. vIGA-AD™. 2017.

44. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology. 1993;186(1)**:**23-31.

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

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

47. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3)**:**199-208.

48. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5)**:**353-365.

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

50. FDA. Food and Drug Administration. Patient-Focused Drug Development Guidance Public Workshop. Methods to Identify What is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments. 15-16 Oct. 2018.

51. Peterson BT, Anderer P, Moreau A, Ross M, Thusoo S, Clare G, Malow B. A novel actigraphy data analysis tool and its application to identifying the optimal threshold value in three subject populations. Physiol Meas. 2016;37(7):N49-61.

52. Moreau A, Anderer P, Ross M, Cerny A, Almazan TH, Peterson B, Moreau A, Anderer P, Ross M, Cerny A, et al. Detection of Nocturnal Scratching Movements in Patients with Atopic Dermatitis Using Accelerometers and Recurrent Neural Networks. IEEE J Biomed Health Inform. 2018;22(4):1011-1018.

53. Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. Sleep Med. 2001;2(5):389-396.

54. Barbier N, Paul C, Luger T, Allen R, De Prost Y, Papp K, Eichenfield LF, Cherill R, Hanifin J. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical trials programme. Br J Dermatol. 2004;150(1):96-102.

55. Cowden JM, Zhang M, Dunford PJ, Thurmond RL. The histamine H4 receptor mediates inflammation and pruritus in Th2-dependent dermal inflammation. J Invest Dermatol. 2010;130(4):1023-1033.

56. Bäumer W, Wendorff S, Gutzmer R, Werfel T, Dijkstra D, Chazot P, Stark H, Kietzmann M. Histamine H4 receptors modulate dendritic cell migration through skin--immunomodulatory role of histamine. Allergy. 2008;63(10):1387-1394.

57. Ling P, Ngo K, Nguyen S, Thurmond RL, Edwards JP, Karlsson L, Fung-Leung WP. Histamine H4 receptor mediates eosinophil chemotaxis with cell shape change and adhesion molecule upregulation. Br J Pharmacol. 2004;142(1):161-171.

58. Hofstra CL, Desai PJ, Thurmond RL, Fung-Leung WP. Histamine H4 receptor mediates chemotaxis and calcium mobilization of mast cells. J Pharmacol Exp Ther. 2003;305(3):1212-1221.

59. Dunford PJ, O'Donnell N, Riley JP, Williams KN, Karlsson L, Thurmond RL. The histamine H4 receptor mediates allergic airway inflammation by regulating the activation of CD4+ T cells. J Immunol. 2006;176(11):7062-7070.

60. FDA. The Food and Drug Administration. Guidance for Industry and Investigators. Safety Reporting Requirements for INDs and BA/BE Studies. 2012.

61. FDA. The Food and Drug Administration. Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse Event Reporting to IRBs - Improving Human Subject Protection. 2009.

62. Institute NC: Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. US Department og Health and Human Services. National Institutes of Health - National Cancer Institute; 2017.

63. European Parliament Union, European CoT: Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, 2001. (EMA ed. 2001.

64. Pharma L: Clinical trial report (CTR) - LP0162-1325 ECZTRA 1 (ECZema TRAlokinumab trial no.1): A randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab monotherapy in subjects with moderate-to-severe atopic dermatitis who are candidates for systemic therapy. 2020.

65. Pharma L: Clinical trial report (CTR) - LP0162-1326 ECZTRA 2 (ECZema TRAlokinumab trial no. 2): A randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab monotherapy in subjects with moderate-to-severe atopic dermatitis who are candidates for systemic therapy. 2020.

66. Rubin DB. Estimating causal effects of treatments in randomized and nonrandomized studies. Journal of Educational Psychology. 1974;66(5):688-701.

67. Parra CO, Daniel R, Bartlett J: **Hypothetical estimands in clinical trials: a unification of causal inference and missing data methods.** 2021

68. Ge M, Durham LK, Meyer RD, Xie W, Thomas N. Covariate-Adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences. Drug Information Journal. 2011;45(4)**:**481-493.

69. ICH. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Clinical Safety Data Management. Definitions and Standards for Expected Reporting (E2A), Step 4; 27-Oct. 1994.

70. CIOMS: International Ethical Guidelines for Health-related Research Involving Humans. Council for International Organizations of Medical Sciences. 4th. Geneva. 2016.

71. EFPIA: European Federation of Pharmaceutical Industries and Associations. Principles for Responsible Clinical Trial Data Sharing. 2013.

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 unfavorable 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 (69).

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavorable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures*.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 11.4.4.2).

Serious adverse event definition

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening – at risk of death at the time of the SAE (not an event that hypothetically might have caused death if more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization*.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.

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

Additionally, all malignancies, including skin malignancies, should be reported as SAEs.

*Hospitalization for procedures or treatments planned prior to the subject consented to trial participation does not constitute an AE and should therefore not be reported as AE or SAE.

Hospitalization for elective treatment of a pre-existing condition which did not worsen from the subject consented to trial participation is not considered an AE and should therefore not be reported as AE or SAE, even if not planned before consent to trial participation.

Hospitalization for routine scheduled treatment or monitoring not associated with any aggravation of the condition does not constitute an AE and should therefore not be reported as AE or SAE.

Hospitalization for administrative purpose does not constitute an AE and should therefore not be reported as AE or SAE.

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event is an SAE.

When in doubt as to whether hospitalization occurred, the AE should be considered serious.

Adverse events of special interest definition

An AESI (serious or non-serious) is an event type of scientific and medical concerns specific to the product or development program, for which additional monitoring may be appropriate. Such an event may warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the investigator to the sponsor and/or from the sponsor to other parties (e.g. regulators) may also be warranted.

AEs considered AESIs in this trial 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 AE worsens in severity, the new severity including date of worsening should be recorded. However, if an AE with onset prior to IMP initiation worsens after first dose of IMP, a new AE should be recorded.

Causality

The *causal relation* of the AE to the use of the IMP should be described in terms of probably, possibly, 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 an SAE, the sequelae should be specified.
Fatal	The subject has died as a consequence of the event. Date of death is recorded as stop date for the AE.
Unknown	Unknown to investigator, e.g. subject lost to follow up.

LEO Pharma definitions versus CDISC definitions

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.

In summary, the definitions used by LEO Pharma are more conservative than those used by CDISC.

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 (32) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (70).
- Current version of applicable International Council for Harmonization Good Clinical Practice (ICH GCP) Guidelines (33).
- EU General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

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

Any documents that the IRB/IEC may need to fulfil its responsibilities (such as the trial protocol, protocol amendments, investigator's brochure, subject information sheet, and 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 favorable 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 ensuring adherence to applicable national and international legislation.

Appendix 3B: Informed consent process

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

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

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

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

Subject card

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

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 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 authorized personnel appointed by LEO Pharma, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Trial subjects must be informed that LEO Pharma might keep their trial-related data for as long as they are useful for developing treatments for the disease or other diseases and future research.

Processing of personal data
This protocol specifies the personal data on trial subjects (e.g. race, ethnicity [if collection is allowed by local legislation], age, sex, 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. 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 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 authorizations for products/services, marketing of products/services, and other related activities.

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

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

Source data at trial sites

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 and dated by medically qualified investigators.

The date and time of sampling must be recorded on the laboratory requisition form.

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:

- Subject ID.
- Randomization code number.
- The fact that the subject is participating in a clinical trial in atopic dermatitis including treatment with LEO 152020 for 16 weeks.
- Other relevant medical information.

Trial monitoring

The trial will be monitored on an ongoing basis to verify that (i) the rights and well-being of the trial subjects is protected; (ii) the reported trial data are accurate, complete, and verifiable from source documents; and (iii) the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP, and all applicable regulatory requirement(s).

The monitoring will be performed in a systematic, prioritized, risk-based approach, and as a combination of on site, remote, and centralized monitoring. For more details, please refer to the trial-specific monitoring guideline and data review plan.

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

Protocol compliance
Protocol deviations will be documented and notified to the investigator. Protocol deviations will be assessed by LEO Pharma and major protocol 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 Pharma must be notified immediately.

Data handling
Data will be collected by means of electronic data capture unless transmitted electronically to LEO Pharma or designee (e.g. laboratory data). The investigator or staff authorized by the investigator will enter subject data into an electronic CRF (eCRF). Data recorded in the eCRF will be accessible to the trial site and LEO Pharma personnel immediately after entry. The eCRF 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 the eCRF. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorized site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require 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 (eDiary data and data from questionnaires completed at the trial site). This solution allows data to be available immediately after entry to site staff, including the investigator, and CRAs 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.

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

Transmissions of data are documented in more detail in a data flow plan which is part of the trial master file.

Statistical programming standards
CDISC controlled terminology version 30-Mar-2018 or newer was used for definition of controlled terminology used throughout this protocol. Standard data tabulation model (SDTM) version 1.4 will be used for data tabulations.

Archiving of trial documentation
The investigator at each trial site must make arrangements to store the essential trial documents, including the investigator trial file (33). 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 (e.g. 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, ePRO, and eDiary data for all screened subjects at the trial site. This is done after completion of the trial and before access to the eCRF/ePRO/eDiary data is revoked. Audit trail information will be included. eCRFs and ePRO/eDiary data must be available for inspection by authorized 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 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 leopharmatrials.com in accordance with our Position on Public Access to Clinical Trial Information within approximately 12 months of 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.

Publications

A publication can be a journal manuscript, an abstract, a poster/presentation for a congress, or any openly accessible material.

A primary publication including the primary results of the trial (i.e. the results of the primary endpoint[s]) may be submitted for peer-reviewed publication within 12 months of database lock. In such case, LEO Pharma would be responsible for this publication. All authors (trial responsible employees and/or applicable investigators and advisors) must fulfill the criteria for authorship from the International Committee of Medical Journal Editors (ICMJE).

The investigators may reach out to LEO Pharma to publish results that are not included in the primary publication. The investigator and LEO Pharma should agree on terms for data sharing and collaboration on such publications, as well as timing for release of the publication(s). In all cases, LEO Pharma retains the right to review and comment on the draft publication in due time before submission, but the investigator is not required to revise the draft accordingly, unless it discloses company confidential information or protected personal information, or may compromise intellectual property rights of LEO Pharma.

LEO Pharma may give researchers outside LEO Pharma access to anonymized data from this trial for further research according to the principles outlined by the European Federation of Pharmaceutical Industries and Associations (EFPIA) (71). In that case, the researchers are obliged to attempt publication of the results obtained from their analyses.

LEO Pharma follows Good Publication Practice (GPP3) standards and the recommendations from ICMJE.

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 and update this information, should any relevant change occur, 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: Committee structure

Subject safety will carefully be assessed by an independent DMC. All members of the DMC will be independent of the trial (i.e. they will not be investigators or employees at participating sites) and of LEO Pharma (i.e. they will not be LEO Pharma employees). The DMC members will be experienced with clinical trial conduct and have expertise from different scientific areas relevant to the trial. The DMC will be responsible for evaluating subject safety through assessment of the safety of the treatment regimens during the trial and through monitoring of the overall conduct of the trial.

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

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

The chairman of the DMC will, in conjunction with the other members, communicate their recommendations to relevant representatives from the clinical trial team at LEO Pharma A/S in an open wrap-up session after each meeting. After each meeting, the chairman of the DMC will provide LEO Pharma with a signed (by the DMC Chair) written DMC recommendation regarding safety concerns and trial continuation. Details on all aspects related to the DMC will be provided in the DMC charter.

Appendix 3I: Trial and trial site closure

Premature termination of trial or trial site

LEO Pharma, the investigator, the IRBs/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 IRBs/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 unfavorable for the continuation of the trial.

Reasons for the premature 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.

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

Appendix 3J: Responsibilities

The signatory investigator is responsible for the approval of the clinical trial protocol and the clinical trial report 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 related to the clinical trial as agreed to in a national coordinating investigator agreement.

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

Appendix 4: Country-specific requirements

This appendix describes country-specific requirements and procedures. For each item below, the original protocol text is in regular font and the country-specific changes ~~crossed out~~ (deleted text) or **bold** (text applicable in the country in question).

GERMANY

Section 5.5 Benefit/risk assessment In Germany, the following edited text will apply: To further ensure subject safety, subjects with cardiac arrhythmic risk factors, moderate or severe hepatic impairment, and/or ~~severe~~ renal impairment will be excluded from participation in the trial (Section 8.3).
Section 8.3 Exclusion criteria In Germany, exclusion criterion 16 will be: Subjects with ~~severe~~ renal impairment as determined by eGFR levels below ~~30~~**90** mL/min at screening.
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. SAEs occurring after the completion of the clinical trial should not be routinely sought or recorded. However, such events should be reported to Global Safety at LEO Pharma (see contact details above) if the investigator becomes aware of them. **In Germany, the following text will apply:** **Any SAE must be reported to LEO Pharma on the (paper) SAE form immediately without undue delay.** **SAEs occurring after the completion of the clinical trial should not be routinely sought or recorded. However, such events should be reported immediately without undue delay to Global Safety at LEO Pharma (see contact details above) if the investigator becomes aware of them.**

JAPAN

Section 5.5 Benefit/risk assessment

To further ensure subject safety, subjects with cardiac arrhythmic risk factors, moderate or severe hepatic impairment, and/or severe renal impairment will be excluded from participation in the trial (Section 8.3).

In Japan, subjects with renal impairment will not be included in the trial:
To further ensure subject safety, subjects with cardiac arrhythmic risk factors, moderate or severe hepatic impairment and/or renal impairment will be excluded from participation in the trial (Section 8.3).

Section 8.2 Inclusion criteria

Inclusion criterion 1
Signed and dated informed consent obtained prior to any protocol-related procedures.

In Japan, if the subject is less than 20 years old prior to 01-Apr-2022, the legal representative must sign the informed consent.

Inclusion criterion 2
Adult, age 18 years or older at screening.

In Japan, inclusion criterion 2 will be: Japanese adults, age 18 years or older at screening.

Inclusion criterion 5
Recent (within 6 months prior to baseline) documented history of inadequate response to topical AD treatments* or subject for whom topical AD treatments are medically inadvisable.

*Inadequate response to topical AD treatments is defined as failure to achieve and maintain remission or a low disease activity state corresponding to 0 (clear) ≤ IGA ≤ 2 (mild) despite treatment with a daily regimen of TCS of medium to high potency (±TCI, as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g. 14 days for super-potent TCS).

In Japan, a list of TCS medications which are considered medium to high in potency will be provided as a separate document to the investigators to aid eligibility assessment. Exclusion criterion 16 Subjects with severe renal impairment as determined by eGFR levels below 30 mL/min at screening. **In Japan, subjects with renal impairment will not be included in the trial. Exclusion criterion 16 will be:** **Subjects with renal impairment as determined by eGFR levels below 90 mL/min at screening.**
Section 9.8.4 Accountability of the investigational medicinal products The investigator is fully responsible for the IMPs at the trial site and for maintaining adequate control of the IMPs and documenting all transactions with them. **In Japan, the Head of Institute will be responsible for the IMPs at the trial site.**
Section 9.10 Reporting product complaints Global Safety, LEO Pharma contact information for reporting product complaints: E-mail address: drug.safety@leo-pharma.com. Fax number: +45 7226 3287. **In Japan, product complaints must be reported to Pharmacovigilance, LEO Pharma K.K. using the contact information below:** **E-mail address: clinical_trial_jp@leo-pharma.com.** **Fax number: +81 3 4243 3311.** **Note: Reports sent to the above email address and fax number will be manually forwarded to Global Safety, LEO Pharma.**

Section 11.1 Overview Subjects participating in the trial will be under the careful supervision of a principal investigator who must be a dermatologist or allergist. Investigators must be physicians and have experience in treating atopic dermatitis as well as documented experience with and/or training in the assessments used in the trial. **In Japan, investigators must be board-certified dermatologists.**
Section 11.4.3 Electrocardiography Between baseline and Week 16, at the visits indicated in Section 4, pre-dose ECGs must be measured shortly before dosing and post-dose ECGs must be measured CCI after dosing. **In Japan at the request of PMDA, 1 additional ECG will be measured at baseline and Week 1, CCI after dosing.**
Section 11.7.2 Wristband scratch and sleep monitoring **In Japan, the optional wristband actigraphy component of the trial will not be available.**
Section 13.4.1 Investigator reporting responsibilities 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 7226 3287. **In Japan, SAEs must be reported to Pharmacovigilance, LEO Pharma K.K. using the contact information below:** **E-mail address: clinical_trial_jp@leo-pharma.com.** **Fax number: +81 3 4243 3311.** **Note: Reports sent to the above email address and fax number will be manually forwarded to Global Safety, LEO Pharma.**

Section 13.4.2 LEO Pharma reporting responsibilities

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.

In Japan, Pharmacovigilance, LEO Pharma K.K. will notify the regulatory authorities and concerned investigators of SAEs.

Section 13.5.1 Pregnancy

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.

In Japan, any pregnancy must be reported to Pharmacovigilance, LEO Pharma K.K. using the contact information below:
E-mail address: clinical_trial_jp@leo-pharma.com.
Fax number: +81 3 4243 3311.

Note: Reports sent to the above email address and fax number will be manually forwarded to Global Safety, LEO Pharma.

Appendix 5: Short version of eligibility criteria and justification

Inclusion criteria		
No.	**Short version**	**Justification**
1	Signed and dated informed consent obtained prior to any protocol related procedures	GCP requirement
2	Adult, age 18 years or older at screening	The trial will be conducted in adults only.
3	Diagnosis of chronic AD as defined by the Hanifin and Rajka (1980) criteria for AD	To ensure correct diagnosis of AD and rule out differential diagnosis
4	History of AD ≥1 year prior to baseline	To ensure inclusion of subjects with chronic AD which is the target population for this trial
5	Recent (within 6 months prior to baseline) documented history of inadequate response to topical AD treatments or subject for whom topical AD treatments are medically inadvisable	To ensure that the subject is candidate for systemic AD treatment
6	7.1≤ EASI ≤50 at baseline	To ensure inclusion of subjects within the entire range of moderate to severe AD but exclude subjects with a very severe disease as there is a high risk that treatment of this population with placebo would not be tolerated
7	vIGA-AD score ≥3 at baseline	To ensure inclusion of subjects with moderate to severe AD and that the subject has a disease severity allowing assessment of improvement
8	BSA ≥5% at baseline	To ensure that the subject has sufficient lesional skin area to assess AD severity
9	Subject agrees to apply an emollient to lesional and non-lesional skin at least twice daily for at least 7 consecutive days immediately prior to baseline.	To keep the subject's skin well-moisturized in the absence of systemic and/or topical AD treatment(s)
10	Women of childbearing potential must use highly effective contraception from randomization to the end of the trial (safety follow-up visit).	To avoid exposing an embryo to LEO 152020 as only nonclinical data on effect of LEO 152020 on reproduction are currently available

Exclusion criteria		
No.	**Short version**	**Justification**
1	Concurrent skin disease at baseline which may interfere with the trial assessments, at the discretion of the investigator	To avoid interference with the trial assessments
2	Active skin infection or any other clinically apparent infection at baseline which may interfere with the trial assessments, at the discretion of the investigator	To avoid interference with the trial assessments
3	Previous treatment with an oral H4R antagonist (including LEO 152020)	The trial will evaluate the effect of LEO 152020 in subjects who have never been exposed to a drug with the same mode of action
4	Previous treatment with 3 or more systemic AD treatments prior to screening	The primary objective of the study is to investigate the exposure-response of LEO 152020. Subjects who have been treated with 3 or more systemic AD treatments could be resistant to any systemic AD treatment. Therefore, these subjects may not benefit from treatment with LEO 152020 and their data may not inform the primary objective of the trial.
5	Systemic treatment including systemic corticosteroids known or suspected to have an effect on AD within 4 weeks or 5 half-lives prior to baseline, whichever is longer	To ensure that previous AD treatments are washed out and do not interfere with trial assessments at baseline
6	Phototherapy within 4 weeks prior to baseline	To ensure that residual effect of phototherapy is avoided and does not interfere with trial assessments at baseline
7	Positive HBsAg, anti-HBs, anti-HBc, or HCV serology at screening	To ensure subject safety by avoiding inclusion of subjects with immune-compromised state and/or latent infections
8	Current active tuberculosis based on test per local standard at screening.	To ensure subject safety by avoiding inclusion of subjects with immune-compromised state and/or latent infections
9	Infection with HIV	To ensure subject safety by avoiding inclusion of subjects with immune-compromised state and/or latent infections
10	History of lymphoproliferative disease or malignancy (except treated and recovered non-melanoma skin cancer or cervical carcinoma in situ) within 5 years prior to screening	To ensure subject safety by avoiding inclusion of subjects with immune-compromised state
11	Subjects at risk for Torsade de Pointes	To ensure subject safety by avoiding inclusion of subjects with cardiac arrhythmic risk factors.
12	Use within 5 half-lives prior to screening of concomitant medication for which QT prolongation is a known side effect and which cannot be discontinued or replaced by (a) safe alternative medication(s)	To ensure subject safety by minimizing possible risk of QT prolongation

13	Resting QTcF (average of a triplicate measurement) < 300 ms or >450 ms (men) or >460 ms (women) at screening	To ensure subject safety by avoiding inclusion of subjects with prolonged QT interval
14	Known history of ventricular arrhythmias	To ensure subject safety by avoiding inclusion of subjects at risk of experiencing cardiac side effects
15	Second- or third degree- atrioventricular block	To ensure subject safety by avoiding inclusion of subjects at risk of experiencing cardiac side effects
16	Subjects with severe renal impairment as determined by eGFR levels below 30 mL/min at screening	To ensure subject safety by excluding the most fragile subgroup of subjects with severe renal impairment
17	Subjects with medical history of chronic moderate to severe liver disease	To ensure subject safety by excluding subjects with potential impaired ability to excrete LEO 152020
18	Clinically significant abnormal finding at screening and/or baseline	To ensure subject safety
19	Any unstable medical, surgical, psychiatric, or additional physical disorder at any time during the trial	To ensure subject safety
20	Known or suspected hypersensitivity to any components of the IMPs or to drugs of a similar chemical class	To avoid allergic reactions to LEO 152020
21	Treatment with any non-marketed drug substance within 4 weeks or 5 half-lives of the drug prior to baseline, whichever is longer	To ensure subject safety and avoid interference with the trial assessments
22	Current participation in any other interventional clinical trial	To ensure subject safety and avoid interference with the trial assessments
23	Previously screened in this trial	To ensure the integrity of the trial. However, rescreening is allowed in case the reason for the screening failure was administrative (Section 8.4)
24	Current or recent chronic alcohol or drug abuse within 12 months prior to screening	To ensure subject safety and avoid inclusion of subjects anticipated to have a challenge completing the trial
25	Subjects, who, in the opinion of the investigator, would be noncompliant or unable to understand the trial and give adequately informed consent	To exclude potentially noncompliant subjects and subjects not able to provide adequately informed consent
26	Employees of the trial site, any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals	GCP requirement
27	Subjects who are legally institutionalized	To avoid inclusion of subjects not able to provide fully informed consent
28	Women who are pregnant, intend to become pregnant, or are lactating	To avoid exposing an embryo/newborn to LEO 152020 as only nonclinical data on effect of LEO 152020 on fetal development/lactation in are currently available

Appendix 6: Contact list

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

Sponsor

LEO Pharma A/S (referred to as 'LEO 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

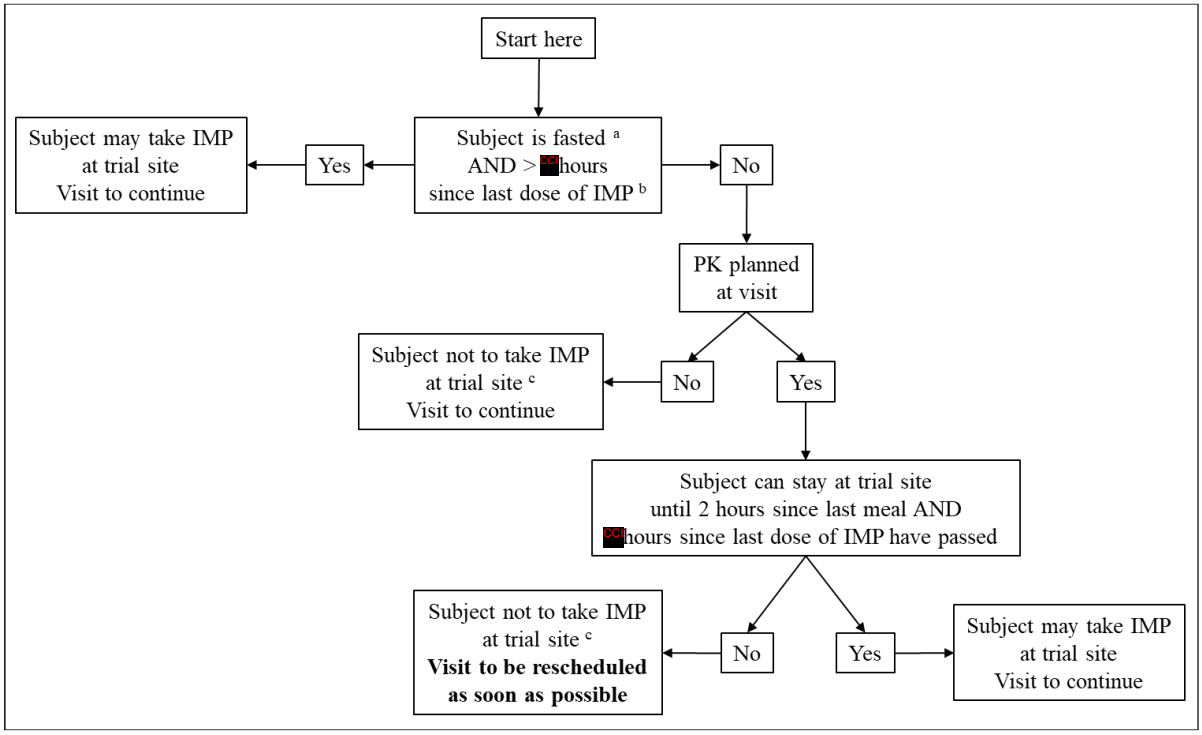
Coordinating investigator

PPD, MD

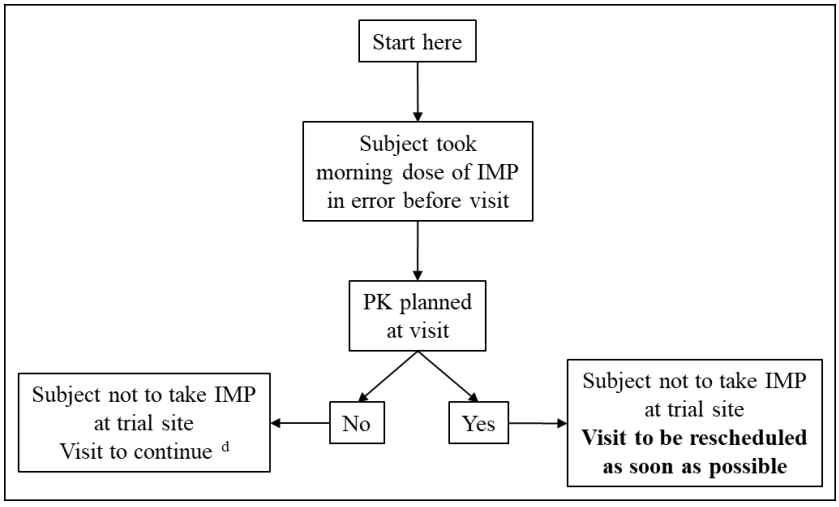
PPD
Hannover
Germany

Appendix 7: Guidance to trial site before subject administers investigational medicinal product at site

Panel 20: a) Is the subject fasted and are there more than [redacted] hours since last dose of IMP?



b) If the subject took a morning dose of IMP in error before the visit



Abbreviations: ECG = electrocardiogram; IMP = investigational medicinal product; PK = pharmacokinetic(s).

[a] Last meal taken more than 2 hours prior to arrival at trial site.

[b] Last dose of IMP taken more than [redacted] hours prior to the dose of IMP at trial site.

[c] See Section 9.2, If the subject misses a visit or a dose of IMP at the trial site. The subject may take the IMP at home and a note of this should be recorded in the subject's record.
[d] If the subject took a morning dose of IMP in error before the visit, efforts should be made to measure the ECG within CCI of IMP intake.

Appendix 8: Prohibited medications (CCI , CCI , and CCI)

Panel 21: List of prohibited medications known to inhibit the CCI

Medication	Therapeutic class
CCI	Antianginal
CCI	FXR agonist
CCI	Angiotensin II inhibitor (angiotensin receptor blocker)
CCI	Other immunomodulator

Abbreviations: CCI ; FXR = potent farnesoid X receptor.

Panel 22: List of prohibited medications known to inhibit the CCI

Medication	Therapeutic class
CCI	Antiarrhythmic
	Calcium channel blocker
	HMG-CoA reductase inhibitor (statin)
	Antibiotic
	Antiviral
	Antipsychotic
	Sodium-dependent glucose cotransporter 2 inhibitor
	Alpha/beta adrenergic antagonist
	Antibiotic
	H1 receptor antagonist
	Antibiotic
	Calcium channel blocker
	Antiarrhythmic
	Gonadotropin-releasing hormone receptor antagonist
	Antibiotic
	Central nervous system agent
	SSRI
	Syk-inhibitor
	Antifungal

Medication		Therapeutic class
CCI		Other antiparkinsonian
		Antifungal
		Other respiratory system products
		Antifungal
		Antiviral
		Opioid
		Beta3-adrenergic agonist
		NSAID
		Serotonin modulator
		Antifungal
		Proton pump inhibitor
		Proton pump inhibitor
		SSRI
		Antiarrhythmic
		Antifungal
		Antiparasitic
		Antiarrhythmic
		Antiarrhythmic
		Antianginal
		Antibiotic
		Antipsychotic
		Antiemetic
		Antibiotic
		Hypnotic (sedative)
		Alpha/beta adrenergic antagonist
		Antibiotic
		CFTR potentiator
		Anticoagulant and antiplatelet
		Vasopressin antagonist

Medication	Therapeutic class
CCI	Central nervous system agent
	Calcium channel blocker
	Anticoagulants and antiplatelet
	Antifungal

Abbreviations: CFTR = cystic fibrosis transmembrane conductance regulator; H1 = histamine 1; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; NSAID = non-steroidal anti-inflammatory drug; CCI ; SSRI = selective serotonin reuptake inhibitor; Syk = spleen tyrosine kinase.

Panel 23: List of prohibited medications known to inhibit the CCI

Medication	Therapeutic class
CCI	Antiandrogen
	NSAID
	Fibric acid derivative
	NSAID
	HMG-CoA reductase inhibitor (statin)
	Uricosuric
	Antibiotics

Abbreviations: HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; NSAID = non-steroidal anti-inflammatory drug; CCI

Appendix 9: COVID-19 contingency plan

Without compromising subject and site staff safety, it is expected that all efforts will be made to ensure subject attendance to trial visits to conduct important efficacy and safety assessments.

As protective/preventive measures can differ across countries and regions, no general instructions from the sponsor can be provided and the investigators will be trusted to take appropriate actions. This includes but is not limited to complying with local regulations and recommendations, increasing protective safety and hygiene measures (e.g. social distancing, wearing mask, disinfecting hands) for both subject and site staff, and frequently monitoring the subject's health.

To minimize exposure to COVID-19 in public transportation, LEO Pharma will reimburse travel cost of subjects using taxis or their own vehicle (including parking fees) to commute to and from the trial site.

If on-site visits are not possible, the site should postpone screening and randomization of subjects until on-site visits can be conducted again. For subjects already randomized in the trial, safety monitoring is an obligation of LEO Pharma and an on-site visit can be converted into a remote visit by means of a video consultation/telephone call for the primary purpose of safety monitoring. To ensure subject privacy, both investigator and subject should confirm their identity at the start of the remote visit. The date of the remote visit should be documented in the subject's record.

At a remote visit, the following safety data must be collected:

- AEs.
- Concomitant medication and concurrent procedures, including use of rescue medication by the subject.
- If applicable, result of the urine pregnancy test*.

  *If needed, women of childbearing potential will be provided with urine pregnancy tests. They will be asked to take the test prior to the remote visit and inform the investigator of the result at the remote visit. A woman with a positive urine pregnancy test must immediately and permanently discontinue IMP and be withdrawn from the trial. A positive urine pregnancy test must be verified with a serum pregnancy test at a local laboratory.

If applicable, the subject will receive a link to complete PROs, which should have been assessed at the trial site, in a web browser (Section 11.5.1). The pandemic is not expected to affect subjects' ability to complete PROs in the eDiary daily (Section 11.5.1). The remote visit must not be used for conducting any investigator's assessments of efficacy.

Continued treatment with the IMP may be allowed if, in addition to the safety assessments listed above, ECG monitoring by a cardiologist and safety laboratory testing can be arranged locally and the results shared with the investigator in time for the nominal safety assessments.

If the above can be arranged, IMP will be shipped to the subject's home and LEO Pharma will provide a shipment solution for return of all (partly) used and unused IMP to the trial site for the purpose of IMP accountability.

If the above cannot be arranged, the investigator or site representative should contact their local monitor and discuss each individual subject case.

If local restrictions preventing the subject from visiting the site are introduced between 2 visits, the subject may continue treatment with the IMP until the scheduled visit as the measures may change favorably prior to that visit. If the measures are still effective at the scheduled visit, the procedures described above should be followed to decide whether the subject may continue dosing with the IMP.

If due to local restrictions, an early termination visit cannot be conducted, a remote safety follow-up visit should be conducted instead. During this visit, AEs, concomitant medications, and concurrent procedures (including use of rescue medication) must be collected. It will be at the discretion of the investigator to conduct other assessments based their local COVID-19 situation.

If at any time during the trial, a subject gets infected with SARS-CoV-2, they should seek appropriate care and inform the investigator or site staff as soon as possible. The infection should be reported as AE. Based on sponsor's evaluation, LEO 152020 is not believed to increase susceptibility of treated subjects to contract COVID-19 and is not expected to decreased anti-viral immunity in infected subjects (Section 5.5). However, decision to continue treatment with IMP of an infected subject should be based on careful evaluation of the subject's condition and will be at the discretion of the investigator. If in doubt or in case of questions, the investigator should contact the sponsor's medical expert.

In general in the context of the COVID-19 pandemic, more frequent telephone contacts between site staff and subjects should be arranged to closely monitor subject safety, treatment compliance, status of subject participation in the trial, and to provide guidance to the subject as to what they will be asked to do in a remote setting to maximize data quality and integrity.

Reporting in eCRF

It will be recorded in the eCRF if a visit or unscheduled visit was conducted remotely. If a trial site visit was not conducted, it will be recorded if this was due to the COVID-19 pandemic. If an unscheduled visit at the trial site is needed due to the COVID-19 pandemic, the reason should be recorded in the eCRF.

Appendix 10: Protocol amendment history

The current protocol amendment (amendment 5) is described before the table of content.

Amendment 4 (30-Nov-2021, local Germany)

This amendment was 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 purpose of this local protocol amendment was to exclude all subjects with renal impairment from participation in the trial in Germany. This was done at the request of the Ethics Committee of PPD (Ethikkommission der PPD).

Summary of changes for amendment 4

Section no. and name	Description of change	Brief rationale
Section 8.3 Exclusion criteria	Exclusion criterion 16 Subjects with severe renal impairment as determined by eGFR levels below 30 mL/min at screening (37). For eGFR levels allowed in **Germany and** Japan, see Appendix 4.	At the request of the Ethics Committee of PPD , subjects with renal impairment will not be included in the trial. This change is to refer to the applicable exclusion criterion 16 in Germany.
Appendix 4 Country-specific requirements	Following items added in subsection 'Germany': In Section 5.5 Benefit/risk assessment, the following edited text will apply in Germany: • To further ensure subject safety, subjects with cardiac arrhythmic risk factors, moderate or severe hepatic impairment, and/or ~~severe~~ renal impairment will be excluded from participation in the trial (Section 8.3). In Section 8.3 Exclusion criteria, the following edited exclusion criterion will apply in Germany: • Subjects with ~~severe~~ renal impairment as determined by eGFR levels below ~~30~~**90** mL/min at screening.	To exclude subject with renal impairment in Germany.

Abbreviations: please refer to the list of abbreviations.

Amendment 3 (06-Oct-2021, global)

This amendment was 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 purpose of the protocol amendment was to:

- Allow data collection after the occurrence of intercurrent events (initiation of rescue treatment and permanent discontinuation of IMP) and incorporate the data when applying the treatment policy strategy to handle these events. The collection of data described is in line with ICH E9 (R1) addendum. Consequently, sections related to rescue treatment, permanent discontinuation of IMP / withdrawal from trial, estimand strategy, and statistical analysis methods were revised.
- Include subjects with mild and moderate renal impairment in the trial.
- Increase monitoring to safeguard subject safety and well-being.
- Update of the contraception requirements for men and women.

Summary of changes for amendment 3

Section no. and name	Description of change	Brief rationale
Section 4 Schedule of trial procedures (Panel 2)	Urine pregnancy test added at the early termination visit.	To ensure women of childbearing potential are tested for pregnancy prior to withdrawing from the trial in case early termination and safety follow-up visits are replaced by a single early termination visit (see also changes in Section 10.3 Early termination assessments).
	Footnotes related to PK blood samples edited and/or merged to refer to Panel 3.	To clarify the order of assessments.
	In footnote starting with 'At the indicated visits, subjects will be asked to bring the wristband actigraphy devices…': ~~The devices can record 30 days of data at a time. Therefore, the time between consecutives visit should not exceed 30 days and special attention should be paid in case of missed visits.~~	Deleted because this will be explained in the actigraphy device manual.
Section 5.2.1 Nonclinical data	Section updated with: • Results from in vitro safety pharmacology screen showing inhibition of acetylcholinesterase by LEO 152020 as well as information about other relevant nonclinical investigations in monkeys showing clinical signs of cholinergic activation. • Results of 26-week rat toxicology study showing [redacted] partially reversible after [redacted] compared to the highest dosing regimen tested in this trial).	To align with updates in the investigator's brochure and provide additional nonclinical context for the new information.

Section no. and name	Description of change	Brief rationale
Section 5.2.2 Clinical data	There were emerging CCI [redacted] **events were classified as mild, occurred rapidly after dosing, and the majority of events resolved within CCI hours.** (…) **Given the mild severity, fast onset, and transient nature of the CCI events, and that the events were primarily observed at the CCI , these events were not considered a safety concern and are not expected to be relevant at the therapeutic doses given in this trial.** (…)	To align with updates in the investigator's brochure.
	The mean effect in the CCI and CCI mg multiple dose groups were CCI and CCI , respectively. **Furthermore, in the multiple dose but not the single dose part of the trial, a dose dependent CCI in heart rate was observed with a CCI decrease of CCI in the CCI mg dose group. In the CCI dose group, the heart rate CCI was CCI (CCI). Thus, it is unlikely that these findings are clinically relevant at the therapeutic doses given in this trial.**	To align with updates in the investigator's brochure.

Section no. and name	Description of change	Brief rationale
Section 5.5 Benefit/risk assessment (Risks for subjects treated with LEO 152020) (Continues)	~~Due to the important potential risk of QT prolongation, the dose regimens explored in this trial have been chosen so that at the highest expected exposure (Cmax), the potential resulting QT prolongation, i.e. the upper bound of the 90% CI for CCI), is below CCI (34).~~ **Due to the CCI the dose regimens explored in this trial have been chosen to minimize that risk for the subjects. The highest dose regimen in the trial (CCI is predicted to result in concentration levels below those of the CCI mg once daily dose regimen, which in the first-in-human trial resulted in a mean CCI of CCI with an upper bound of the 90% CI for CCI at CCI (Section 5.2.2). Since subjects with mild and moderate renal impairment may exhibit increased exposure of LEO 152020, ECGs will be measured at each visit (Section 4) to monitor the individual subjects in line with CCI for drugs for which a CCI cannot be excluded (Panel 2).**	To update mitigation of the CCI as subjects with mild and moderate renal impairment will be included in the trial (see also changes to exclusion criterion 16), except in Japan (see Appendix 4 Country-specific requirements). This is considered acceptable since subjects will be monitored with ECGs taken at every visit.

Section no. and name	Description of change	Brief rationale
Section 5.5 Benefit/risk assessment (Risks for subjects treated with LEO 152020) (Continued)	To further ensure subject safety, subjects with cardiac arrhythmic risk factors, **moderate and severe** hepatic **impairment,** and**/or severe** renal impairment will be excluded from participation in the trial (Section 8.3).	To align with exclusion criterion 17.
	At selected visits, ECG and PK blood samples collected at the same timepoint will be used to explore the relation between exposure of LEO 152020 and potential CCI CCI (Section 4). **In the multiple dose part of the first-in-human trial, a dose-dependent CCI in heart rate was observed with a CCI CCI) in the CCI dose group. If a subject develops CCI and CCI , the risk of CCI may increase. To mitigate this, ECGs will be taken at each visit (Section 4) to monitor all subjects.**	To align with updates in the investigator's brochure and provide further guidance to the investigator.
	In the first-in-human clinical trial, mild CCI adverse events were observed following treatment with CCI LEO 152020. As CCI CCI may increase the risk of CCI , additional monitoring of CCI should be arranged, at the discretion of the investigator, for subjects who experience CCI during the treatment period.	To align with updates in the investigator's brochure and provide further guidance to the investigator.

Section no. and name	Description of change	Brief rationale
Section 6 Trial objectives, estimands, and endpoints Section 14.3.10 Analysis of exploratory endpoints	• EASI at each visit from ~~baseline~~ **Week 1** to Week 16. • SCORAD at each visit from ~~baseline~~ **Week 1** to Week 16.	'Baseline' replaced by 'Week 1' because baseline measures are meant to characterize the subject population and act as reference values for assessing within-subject changes during the trial.
Section 14.3.11 Analysis of patient-reported outcomes Section 14.3.15 Pharmacokinetic analysis (Continues)	• Time **from randomization** to having a**n observed** decrease in EASI of at least 50% (EASI 50) from baseline. • Time **from randomization** to having a decrease in ADSD CCI score (weekly average) of at least 4 points from baseline in subjects with ADSD CCI score ≥ 4 at baseline.	To clarify the reference time point for an observed decrease in EASI and ADSD CCI score.
	• ~~Change in vIGA-AD from baseline to Week 16.~~ • ~~vIGA-AD at each visit from baseline to Week 16.~~	Deleted because it is considered sufficient to include: • Having vIGA-AD of 0 (clear) or 1 (almost clear) at Week 16. • Having a decrease in vIGA-AD of at least 2 points from baseline to Week 16. to support the primary objective.
	• ~~Change in ECG parameters CCI from baseline to Week 12.~~ • ~~ECG parameters CCI at baseline, Weeks 1, 4, and 12.~~	Deleted as endpoint (but not assessments) for this trial because a thorough CCI clinical trial with LEO 152020 is planned to be conducted.
	• ~~PGI-C (each individual component) at Weeks 8, 12, and 16.~~ • ~~PGI-S (each individual component) at baseline and Weeks 4, 8, 12, 14, and 16.~~	Deleted as endpoints (but not assessments) for this trial because those will be used to qualify other PROs. The PROs listed under the objective related to sleep disturbance and nocturnal CCI are considered sufficient to support the objective.

Section no. and name	Description of change	Brief rationale
Section 6 Trial objectives, estimands, and endpoints Section 14.3.10 Analysis of exploratory endpoints Section 14.3.11 Analysis of patient-reported outcomes Section 14.3.15 Pharmacokinetic analysis (Continued)	• C_{trough} of LEO 152020 at ~~baseline,~~ Weeks [redacted] • C_{max} of LEO 152020 at ~~baseline,~~ Weeks [redacted]	Deleted 'baseline' because there can be no C_{trough} at baseline (the subject has not received IMP). 'Baseline replaced by 'Week [redacted]' because baseline values are meant to characterize the subject population and C_{max} will be measured approximately [redacted] after IMP intake at Week [redacted].
Section 7.1 Overall trial design, subsection 'Randomization'	Subsection shortened.	To avoid repetition with Section 9.3.1 Treatment assignment.
Section 7.2 Number of subjects needed Section 1 Protocol synopsis (Trial design [in the figure], Number of subjects) Section 3 Schematic of trial design (Panel 1)	Number (N) of subjects in each treatment group deleted.	The randomization scheme does not ensure that subjects will be allocated in the proportion that was initially specified. However, within each stratum, subjects will still be randomized in a 4:3:3:4 ratio based on a permuted block design.
Section 7.2 Number of subjects needed	~~Based on an anticipated attrition rate of 15% in all treatment groups, this will provide a total of 192 subjects for analysis.~~ ~~A block size of 14 will be used for randomization ensuring a balanced distribution of subjects across the sites.~~	Deleted because all subjects included in the full analysis set, i.e. randomized and exposed to IMP will be included in the analysis. Deleted because this information will be specified in the randomization form to minimize the chance of allocation bias.
Section 7.3 End-of-trial definition	Depending on the DMC's recommendations, LEO Pharma may decide to terminate the trial prematurely in interest of subject safety. ~~In such case, the end of the trial would be defined as the date of trial termination.~~	Because in case of premature trial termination, the trial end is still defined as the date of last visit of the last subject in the trial globally.

Section no. and name	Description of change	Brief rationale
Section 8.2 Inclusion criteria Section 1 Protocol synopsis (Main criteria for inclusion) Appendix 4 Country-specific requirements Appendix 5 Short version of eligibility criteria and justification	Inclusion criterion 2: Adult, age 18 years or older at ~~baseline~~ **screening**.	To ensure that subjects will at least be 18 years at screening when they provide informed consent.
Section 8.2 Inclusion criteria, criteria 10 and 11. Section 5.4 Ethical considerations Appendix 5 Short version of eligibility criteria and justification	Contraception reduced to 1 highly effective contraception method for women of childbearing potential and contraception deleted for male subjects with a partner of childbearing potential.	To reflect the recommendations about contraception of the Clinical Trials Facilitation and Coordination Group (CTFG) guidance v1.1 for IMPs with unlikely human teratogenicity, fetotoxicity, or genotoxicity (see also the investigator's brochure).
Section 8.3 Exclusion criteria, criteria 1 and 2 Appendix 5 Short version of eligibility criteria and justification	Concurrent skin disease at baseline which may interfere with the trial assessments**, at the discretion of the investigator**. Active skin infection or any other clinically apparent infection at baseline **which may interfere with the trial assessments, at the discretion of the investigator**.	To clarify that these 2 eligibility assessments will be left at the discretion of the investigator.
Section 8.3 Exclusion criteria, criterion 8 Section 4 Schedule of trial procedures (Panel 2) Section 11.2.5 Other screening assessments Section 11.4.4 Laboratory testing (Panel 11) Appendix 5 Short version of eligibility criteria and justification	Current active tuberculosis based on ~~mycobacterium tuberculosis IFN gamma response test at screening~~ **test per local standard of care at screening. The screening for tuberculosis should be done according to guidelines for patients subject to biologic treatment as per local standard of care**.	To take into account local differences in standard of care. The new approach is considered equally safe.

Section no. and name	Description of change	Brief rationale
Section 8.3 Exclusion criteria, criterion 11 Section 4 Schedule of trial procedures (Panel 2)	Uncorrected hypokalemia or hypomagnesemia at ~~screening and/or baseline~~ **Week -1**, history of cardiac failure, history of clinically significant/symptomatic bradycardia. Clinical chemistry and hematology blood sample added at Week -1 to reflect the above.	To allow for timely results prior to randomization.
Section 8.3 Exclusion criteria, criterion 16 Appendix 5 Short version of eligibility criteria and justification	Subjects with ~~signs of~~ **severe** renal impairment as determined by eGRF levels below ~~90~~ **30** mL/min at screening ~~and/or baseline~~.	To allow the inclusion of a broader patient population in the trial, except in Japan (see Appendix 4 Country-specific requirements). The inclusion of subjects with mild to moderate renal impairment is considered safe and will be further safeguarded by increasing ECG monitoring to each visit in line with CCI (see also changes to Section 11.4.3 Electrocardiography).
Section 8.3 Exclusion criteria, criteria 24 and 25 Appendix 5 Short version of eligibility criteria and justification	Exclusion criterion 25 added: **Subjects, who, in the opinion of the investigator, would be noncompliant or unable to understand the trial and give adequately informed consent.** Current or recent chronic alcohol or drug abuse~~, or any other condition associated with poor compliance as judged by the investigator~~ within 12 months prior to screening.	To exclude potentially noncompliant subjects and subjects not able to provide adequately informed consent. To avoid redundancy with added criterion 25
Section 8.3 Exclusion criteria, criterion 28 Appendix 5 Short version of eligibility criteria and justification	Women who are pregnant**, intend to become pregnant,** or **are** lactating.	To clarify and avoid pregnancy during the trial.

Section no. and name	Description of change	Brief rationale
Section 9.3.1 Treatment assignment	Subjects who comply with all eligibility criteria (Sections 8.1 to 8.3) will be randomized ~~at baseline~~ to 1 of the following oral treatments ~~in a 4:3:3:4 ratio stratified by baseline disease severity (EASI at baseline) and region (Japan and non-Japanese countries):~~ **Within the strata defined by baseline disease severity (EASI at baseline) and region (Japan, non-Japanese countries), subjects will be randomized in a 4:3:3:4 ratio, using a permuted block design**.	To clarify randomization and stratification.
Section 9.3.2 Blinding Section 12.1 Scientific rationale for trial design	Triple blinding (subject, ~~assessor~~ **investigator**, and **assessor of the data/study outcome [**sponsor**]**) from randomization to formal unblinding of the trial will be applied.	To clarify the extent of blinding.
Section 9.5 Rescue treatment Section 5.5 Benefit/risk assessment	Subjects will be allowed to receive topical rescue treatment during the treatment period with no permanent discontinuation of IMP (nor withdrawal from the trial). The duration of topical rescue treatment and decision to escalate to systemic rescue treatment and when to escalate will be left at the discretion of the investigator. Discontinued subjects due to the use of systemic rescue treatment will no longer be withdrawn from the trial.	To allow subjects who initiates topical rescue treatment prior to Week 4 to continue treatment with IMP and remain in the trial. Further, to allow collection of data after initiation of rescue treatment and discontinuation of IMP.

Section no. and name	Description of change	Brief rationale
Section 9.5 Rescue treatment	~~Immediately b~~ **B**efore administering ~~a~~ **topical or** systemic rescue treatment, the investigator ~~should make every attempt to~~ **may** conduct efficacy and safety assessments (e.g. disease severity scores [EASI, vIGA AD, and SCORAD], AEs, safety laboratory samples, PK blood sample, and concomitant medications/concurrent procedures). ~~If necessary~~ **However, to safeguard subject safety and well-being, the assessments should only be conducted if the subject's health permits. To further attend to subject safety and well-being**, an unscheduled visit ~~should~~**, scheduled earlier than the next planned visit, may** be arranged ~~for this purpose~~ **to administer the topical or systemic rescue treatment**.	To clarify conditions for conducting assessments before administering rescue treatment and that an unscheduled visit may be used to provide diligent attention to the subject.
	If the subject is ~~withdrawn from the trial~~ **permanently discontinued from IMP** due to use of **systemic** rescue medication, ~~the subject should be followed up~~ **every effort must be done to monitor the subject** as described in Section 10.3.	To align with other changes in Section 9.5 Rescue treatment (see entry above) and clarify follow up of discontinued subjects.
Section 9.6 Concomitant medications and concurrent procedures Section 10.2 Reasons for permanent discontinuation of investigational medicinal product (Reporting in eCRF) Section 11.8 End of trial (End-of-trial form)	Specifications of the reasons for lack of efficacy of the IMP added: • **Lack of efficacy on itch.** • **Lack of efficacy on visible AD symptoms.** • **Lack of efficacy on both itch and visible AD symptoms.** • **Other (if other, a specification should be provided).**	To gain knowledge of whether the lack of efficacy is related to lack of effect of the IMP on itch and/or visible AD symptoms.
Section 9.6 Concomitant medications and concurrent procedures	Investigators may prescribe concomitant medications or treatments to provide adequate supportive care, at their discretion. (…) ~~Any questions about concomitant or prior therapy should be addressed to the sponsor's medical expert.~~	While some decisions will be left at the discretion of the investigator, it is implicit that they are welcome to consult the sponsor's medical expert, if needed.

Section no. and name	Description of change	Brief rationale
Section 9.7 Prohibited medications and procedures (Panel 7)	Footnote to systemic anti-histamines added: **Locally-administered anti-histamines (e.g. eye drops, nasal spray) are allowed.** Footnote to topical antibiotics added: **Except if used on small lesional areas**	To clarify that locally-administered anti-histamines will be allowed during the trial. To clarify that topical antibiotics may be used to small lesional areas
Section 9.8.3 Storage of trial products	~~At the subject's home, the IMP should be stored below 40°C/104°F and should not be stored in the fridge or freezer.~~ Storage of the IMP at the subject's home will be described in separate instructions for use for the subject to take home.	Deleted as the storage of the IMP at the subject's home will be described in the IMP instruction for use.
Section 9.8.5 Treatment compliance	~~For IMP taken at the site, date and time of IMP intake will be recorded in the eCRF.~~ **It will be recorded in the eCRF if IMP was taken at the site. If not, a reason should be provided. If yes, date and time of IMP administration will also be recorded.**	To clarify what data will be collected to evaluate treatment compliance.
Section 10 Discontinuation and withdrawal Section 4 Schedule of trial procedures (Panel 2, footnotes) Section 5.5 Benefit/risk assessment Section 11.4.3 Electrocardiography	The difference between permanent discontinuation of IMP and withdrawal from the trial was clarified. Permanent discontinuation of IMP and withdrawal from trial will be 2 separate events and subjects who permanently discontinue IMP will no longer automatically be withdrawn from the trial. Subjects who permanently discontinue IMP will be asked to attend an early termination visit as soon as possible after last dose of IMP and the nominal primary endpoint visit 16 weeks after first dose of IMP. Subjects who withdraw from the trial will be asked to attend an early termination visit and a safety follow-up visit 7 days after last dose of IMP.	To clarify the difference between permanent discontinuation of IMP and withdrawal from trial and allow collection of post-discontinuation data in line with ICH E9 (R1) addendum.

Section no. and name	Description of change	Brief rationale
Section 10.4 Continued assessment of subjects after permanent discontinuation of investigational medicinal product	Section added. **Subjects who permanently discontinue IMP prior to Week 16 should be encouraged to continue participating in the trial and to follow their visit schedule to the extent possible**.	To allow collection of post-discontinuation data in line with ICH E9 (R1) addendum.
Section 11.4.3 Electrocardiography Section 4 Schedule of trial procedures (Panel 2 and Panel 3) (Continues)	ECG monitoring increased to be conducted at all visits (optional at an unscheduled visit) and footnotes to schedule of trial procedures edited and/or merged to reflect the new monitoring setup.	To safeguard safety of all subjects, including subjects with mild and moderate renal impairment (see also changes to exclusion criterion 16) in line with CCI . CCI [redacted]
	~~At the screening visit, 3 consecutive ECGs must be measured.~~ ~~Between baseline and Week 16, at the visits indicated in Section 4, pre dose ECGs must be measured shortly before dosing and post dose ECGs must be measured~~ CCI ~~after dosing. In Japan at the request of PMDA, 1 additional ECG will be measured at baseline and Week 1,~~ CCI ~~after dosing.~~	Deleted to avoid redundancy with Panel 3.
	The collection of a PK sample was added in case a moderate or severe CCI is detected at visits: **A PK sample (if not already planned at the visit) must be taken close to the last measured ECG.**	Added to study the potential relationship between exposure and QT prolongation.
	If the subject returns to CCI ≤480 ms (mild CCI or normal CCI) **and increase in** CCI **from baseline ≤30 ms**, the ECG and PK monitoring schedule described in Section 4 ~~may~~ **should** be followed again.	To clarify that moderate CCI is defined as either 480 ms< CCI ≤500 ms OR 30 ms< increase in CCI from baseline ≤60 ms.

Section no. and name	Description of change	Brief rationale
Section 11.4.3 Electrocardiography Section 4 Schedule of trial procedures (Panel 2 and Panel 3) (Continued)	~~During the trial~~ **Before first dose of IMP**, any abnormal clinically significant **or clinically relevant** ECG finding **will be documented as medical history in the eCRF. After first dose of IMP, any new abnormal clinically significant or clinically relevant ECG finding**, symptoms, or illnesses, as well as any clinically significant deterioration of a pre-existing condition ~~after randomization~~ will be reported as an AE as described in Section 13.3.	To clarify how ECG findings will be reported in relation to first dose of IMP.
Section 11.4.3 Electrocardiography Section 10.2 Reasons for permanent discontinuation of investigational medicinal product Section 13.6.1 Adverse events of special interest (Panel 14 and footnote)	(…) ~~change~~ **increase** in CCI from baseline (…).	To clarify that only increases in CCI from baseline constitute CCI
Section 11.4.4.2 Investigator evaluation of laboratory samples (Laboratory tests conducted at the trial site) Section 11.2.5 Other screening assessments	Tuberculosis testing will be conducted as per local standard. Added the following in Section 11.4.4.2 and 11.2.5, respectively: **Subjects with a positive tuberculosis test conducted at the trial site at screening should be referred to a competent health care structure for treatment and follow up.** **Tuberculosis testing will be per local standard of care (see exclusion criterion 8). If the tuberculosis test cannot be analyzed locally, it should be sent to the central laboratory.**	To clarify operational considerations regarding tuberculosis testing.
Section 11.6.2 Pharmacodynamic assessments (Blood biomarkers)	~~8 mL of blood will be collected into Vacutainer® tubes to obtain 4 mL of serum which will be stored at ≤ 20°C until shipment to the central laboratory for further processing.~~	Deleted because this will be described in a separate laboratory manual.

Section no. and name	Description of change	Brief rationale
Section 11.7.2 Wristband scratch and sleep monitoring	At each visit between baseline and Week 16, it will be recorded: • **If the subject wore the device as instructed. If not, a reason should be provided.**	To clarify what data will be recorded in the eCRF.
Section 11.7.3 Skin biopsies	~~The biopsies will be transferred to RNAlaterTM solution (for RNA stabilization) immediately after collection and stored at 2-8°C for 16 30 hours. The sample will then be transferred to a clean tube and stored at < 20°C until shipment to the central laboratory for further processing.~~	Deleted as the method for handling skin biopsy samples will be described in a separate laboratory manual.
Section 11.8 End of trial (End-of-trial form)	Data to collect in the eCRF added: **If the subject attended the (nominal) primary endpoint visit (Week 16 or 16 weeks after first dose of IMP). If not, the primary reason for not attending the visit should be provided (death, pregnancy, adverse event, lack of efficacy, withdrawal by subject, lost to follow up, or other [if other, a specification should be provided]).**	To clarify collection of data on the end-of-trial form as permanently discontinued subjects will no longer be automatically withdrawn from trial and asked to come to a nominal primary endpoint visit.
Section 11.9 Estimate of total blood volume collected	Maximum total volume of blood to be collected during the trial updated.	To reflect the samples added in Section 4 Schedule of trial procedures and take into account possible extra PK samples in case the subject experiences a CCI [redacted]

Section no. and name	Description of change	Brief rationale
Section 12.1 Scientific rationale for trial design	Mitigation of bias ~~Stratified randomization according to baseline disease severity (EASI at baseline) will ensure balanced allocation of subjects with CCI ≤ EASI ≤CCI and subjects with CCI ≤ EASI ≤CCI at baseline between the treatment groups, thereby minimizing allocation bias and baseline confounding. Stratification by region (Japan and non-Japanese countries) will ensure balanced allocation of subjects in each region (Section 7.1).~~ **The combination of randomization and blinding minimizes the likelihood of allocation bias. The risk of allocation bias is further reduced through the use of central randomization, i.e. the randomization will not be stratified by site nor will complete blocks be allocated to sites. The use of randomization also ensures that baseline factors will not be confounded with treatment. The use of a permuted block randomization within the strata defined by baseline disease severity (EASI at baseline) and region (Japan and non-Japanese countries) will limit any potential imbalance in the allocation of subjects across these factors (Section 7.1).**	To clarify the mitigation of bias.
Section 12.2 Appropriateness of assessments	Inflammatory markers (cytokines and chemokines) associated with AD (e.g. CCL17, ~~CCL18,~~ sIL-2R, IL-13, IL-22, ~~PBMC, RN6A seq,~~ IgE~~, IgG4~~) will be measured in serum over time to determine AD burden.	To clarify the biomarkers which may be evaluated in this trial.
Section 14.1 Sample size Section 14.3.7 Testing strategy	Sample size justification revised.	To reflect the changes in Section 14.3.8 Analysis of primary endpoint.

Section no. and name	Description of change	Brief rationale
Section 14.3.8 Analysis of primary endpoint Section 1 Protocol synopsis (Statistical methods) Section 12.1 Scientific rationale for trial design (Endpoints and estimands) Section 14.3.3 Handling of intercurrent events related to the COVID-19 pandemic	Estimand strategy revised. The original primary estimand (composite) was exchanged with 1 of the original supplementary estimands (hypothetical) to improve the interpretability of the primary estimand.	To include data collected after occurrence of intercurrent events (initiation of rescue treatment and permanent discontinuation of IMP) in the analysis in line with ICH E9 (R1) addendum. Based on feedback from health authorities. Improving the interpretability of the primary estimand will aid dose-selection for phase 3 clinical development.
Section 14.3.8 Analysis of primary endpoint Section 14.3.10 Analysis of exploratory endpoints	Analysis methods clarified.	To improve the interpretability of the results of the data analysis.
Section 14.3.10 Analysis of exploratory endpoints Section 14.3.2 Handling of missing values Section 14.3.11 Analysis of patient-reported outcomes	Analysis method of binary endpoints changed from CMH test to logistic regression.	To avoid potential invalidity of the analysis method due potential small strata sizes.
Section 14.3.14.3 Electrocardiography	Section added. **Absolute values and change in ECG parameters** CCI [redacted] **from baseline to each relevant visit will be summarized by treatment group as mean, SD, median, minimum and maximum values for the safety analysis set.** **Subjects with abnormal clinically significant ECG parameters will be listed. Furthermore, a shift table showing the change in clinical assessments (normal, abnormal not clinically significant, abnormal clinically significant) for the ECG parameters from baseline to Week 16 will be provided.**	To clarify presentation of the ECG data.

Section no. and name	Description of change	Brief rationale
Appendix 2 Classification of adverse events	~~If the severity of an AE worsens, a new AE should be recorded.~~ **If the AE worsens in severity, the new severity including date of worsening should be recorded. However, if an AE with onset prior to IMP initiation worsens after first dose of IMP, a new AE should be recorded.**	To collect more accurate information on worsening of AE severity and to ease reporting for the investigator.
Appendix 4 Country-specific requirements	For Germany, text in Section 13.4 Reporting of serious adverse events will read: Any SAE must be reported to LEO Pharma on the (paper) SAE form ~~within 24 hours of first knowledge~~ **immediately without undue delay**. SAEs occurring after the completion of the clinical trial should not be routinely sought or recorded. However, such events should be reported to Global Safety at LEO Pharma (see contact details above) **immediately without undue delay** if the investigator becomes aware of them.	Rephrased at the request of BfArM to abide by German law for timing of SAE reporting in Germany.
	For Japan, text in Section 5.5 Benefit/risk assessment will read: To further ensure subject safety, subjects with cardiac arrhythmic risk factors, **moderate or severe** hepatic **impairment**,~~-~~and/or ~~severe~~ renal impairment will be excluded from participation in the trial (Section 8.3). For Japan, text in Section 8.3 Exclusion criteria, exclusion criterion 16 will read: Subjects with signs of ~~severe~~ renal impairment as determined by eGFR levels below ~~30~~**90** mL/min at screening.	In Japan, subject with renal impairment will not be included in the trial.

Section no. and name	Description of change	Brief rationale
Appendix 7 Guidance to trial site before subject administers investigational medicinal product at site	In Panel 20 a) and b), box ~~ECG/PK planned at visits~~ replaced by **PK planned at visit**. Footnote to Panel 20 b) added: **If the subject took a CCI dose of IMP in error before the visit, efforts should be made to measure the ECG within CCI of IMP intake.**	To update and provide further guidance to the investigator.
Appendix 10 Protocol amendment history	Section added.	To list the local protocol amendments and local addendum to amendment preceding this global amendment.

Abbreviations: please refer to the list of abbreviations.

The global protocol amendment (v3.0) of 06-Oct-2021 includes the changes implemented for Germany (local amendment 1 and addendum 1 to amendment 1) and Czech Republic (local amendment 2). Therefore, the corresponding summary of changes tables for these protocol amendments are not reproduced below (see summary of changes table for amendment 3 above).

Addendum 1 to amendment 1 (05-Aug-2021, local Germany)

Overall rationale for the addendum

This addendum to amended protocol v2.0 DE (30-Jun-2021) was to address comments from the German Federal Institute for Drugs and Medical Devices (BfArM). The purpose of the addendum was to have the timing for reporting of serious adverse events (SAEs) to comply with current German law.

Amendment 2 (07-Jul-2021, local Czech Republic)

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

Overall rationale for the amendment
This protocol amendment was to address comments from the Czech State Institute for Drug Control to v1.0 of the global protocol. The purpose of the amendment was mainly to clarify aspects related to rescue treatment and prior and concomitant medications.

Amendment 1 (30-Jun-2021, local Germany)

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

Overall rationale for the amendment
This protocol amendment was to address comments from the German Federal Institute for Drugs and Medical Devices (BfArM) to v1.0 of the global protocol. The purpose of the amendment was mainly to clarify aspects related to rescue treatment and timing for reporting SAEs.