Clinical Trial Protocol

LP0145-1376

A phase 2a, randomised, double-blind, placebo-controlled, multi-site, proof of concept trial to evaluate the efficacy and safety of LEO 138559 in adult subjects with moderate to severe atopic dermatitis (AD).

Phase 2a Proof of Concept

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:**	**LP0145-1376**
	Date:	**31-Jan-2022**
	EudraCT no:	**2020-005541-16**
	Version:	**4.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

Electronic signatures made within eTMF LEO Pharma are considered to be a 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, MMath, PhD
Biostatistics lead, Medical Sciences

PPD, MD
Vice president, Medical Sciences

PPD, MD, PhD
Vice president, Translational Medicine

PPD, PhD
Clinical operations lead, Global Clinical Operations

PPD, MD
Signatory investigator

Acknowledgement statement investigators

Each participating investigator must agree to the approved clinical trial protocol by signing a clinical trial protocol acknowledgement form or similar document.

Protocol amendment summary

Document history

Document	Date	Type of protocol amendment
Amendment 3 (substantial)	31-Jan-2022	Global
Amendment 2 (non-substantial)	17-Nov-2021	Global
Amendment 1 (substantial)	07-May-2021	Global
Original protocol	12-Mar-2021	NA

Abbreviations: NA = not applicable.

Note that protocol amendment summary of changes tables for the previous amendments are provided in Appendix10.

Amendment 3 (31-Jan-2022)

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

Overall rationale for the amendment

The main purpose for this protocol amendment is to change the event of a positive SARS-CoV-2 test (COVID-19) from leading to permanent discontinuation of IMP (Section 10.2.1) to leading to a possible temporary discontinuation of IMP (Section 10.2.2).

At the time of protocol preparation, COVID-19 was considered a disease with lower respiratory tract involvement in many people infected. However, even though the IL-22R is expressed in the lungs, the role of LEO 138559 in the context of COVID-19 disease was unknown. It was expected that the number of people infected with SARS-CoV-2 during the conduct of the trial would be low, and therefore not anticipated to affect data integrity of the trial. These assumptions led to a conservative approach of permanently discontinuing IMP for subjects testing positive for SARS CoV-2.

During trial conduct, the COVID-19 situation in many countries including Germany, Poland, US, and Canada, has changed. At the beginning of the pandemic, the number of infected patients was lower than now, but with a higher risk of severe illness. Now, a very high number of newly infected people each day is observed (possibly due to a combination of more contagious mutations and a higher test capacity), but with an overall lower number of patients with severe illness (possibly due to the introduction of vaccines and virus variants leading to

milder symptoms in the majority of the infected people). Based on this, a potential safety concern for the patients in relation to SARS CoV-2 infection is now reduced.

The observed development in the SARS CoV-2 infection rates, results in a risk of a potential higher trial attrition rate than previously expected. With the current knowledge of COVID-19 disease course, presenting with many cases of mild disease, it is considered reasonable to not per default discontinue subjects with a SARS CoV-2 infection from IMP treatment. Based on local guidelines and regulations on handling of SARS CoV-2 infection, it is considered relevant to allow temporary, instead of per default permanent discontinuation of IMP similar to other COVID-19 related disruptions (Section 10.2.2 and Appendix 9). Note that as per investigator discretion, the IMP can still be permanently discontinued.

Introducing this amendment increases the possibility of retaining patients in the trial, thereby fulfilling our ethical obligation to all the participating subjects and investigators. Furthermore, the amendment does not affect the total number of subjects, statistical analysis, and interpretation of the trial results, and has no impact on patient safety, thus no impact on the scientific value or integrity of the trial.

All changes to the protocol are presented in the summary of changes table below except for a few minor editorial changes (e.g. spelling errors).

Summary of changes

Section no. and name	Description of change	Brief rationale
Section 9.10 Reporting product complaints	Fax number: +45 ~~7226 3287~~**6910 2468**	Editorial.
Section 10.2.1 Reasons for permanent discontinuation of IMP	~~• Infection with SARS-CoV-2 (COVID-19).~~	Due to change in the global SARS CoV-2 (COVID-19) situation.
Section 10.2.2 Reasons for temporary discontinuation of IMP	• COVID-19 related disruption ~~leading to site closure~~.	Due to change in the global SARS CoV-2 (COVID-19) situation.
Section 13.4.1 Investigator reporting responsibilities	Fax number: +45 ~~7226 3287~~**6910 2468**	Editorial.
Appendix 3C Subject and data confidentiality	Processing of personal data on behalf of LEO Pharma requires a written agreement between LEO Pharma and the relevant party which covers collection, processing, and transfer of personal data in the clinical trial **as well as reporting obligations in the event of any data breach**. In certain cases, an agreement on transfer of personal data may also be required.	Editorial.

Section no. and name	Description of change	Brief rationale
Appendix 9 COVID-19 pandemic contingency plan	~~A subject testing positive for COVID-19 after randomisation must be permanently discontinued from IMP and withdrawn from the trial.~~ **A subject testing positive for COVID-19 after randomisation may be temporarily discontinued from IMP. IMP treatment may be reinstituted at the investigator's discretion.**	Due to change in the global SARS CoV-2 (COVID-19) situation.
Appendix 10 Protocol amendment history	Protocol amendment 2, Summary of changes table moved to Appendix 10.	Editorial.
Appendix 10 Protocol amendment history	Amendment 2 (1~~9~~7-Nov-2021)	Editorial.

Table of contents

List of panels

List of abbreviations

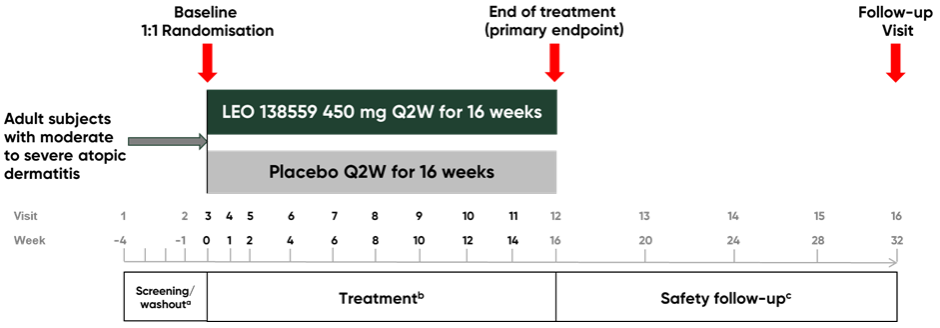
AAD	American Academy of Dermatology
Ab	antibody
AD	atopic dermatitis
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
BCC	basal cell carcinoma
BP	blood pressure
BMI	body mass index
BSA	body surface area
CCL17	chemokine (C-C motif) ligand 17
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
CMO	contract manufacturing organisation
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPM	clinical project manager
CRA	clinical research associate
CRO	contract research organisation
CTR	clinical trial report
DLQI	Dermatology Life Quality Index
DPP4	dipeptidyl peptidase-4
EASI	Eczema Area and Severity Index
EASI 50	at least 50% reduction in EASI score
EASI 75	at least 75% reduction in EASI score
EASI 90	at least 90% reduction in EASI score
ECG	electrocardiogram
eCRF	electronic case report form

eDiary	electronic diary
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
EU	European Union
FAS	Full analysis set
Fc	fragment crystallisable
FDA	Unites States Food and Drug Administration
FiM	first in man
FSFV	first subject first visit
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HbsAg	hepatitis B surface antigen
HCP	healthcare professional
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IEC	independent ethics committee
IFN- γ	interferon gamma
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IL-10R2	interleukin 10 receptor 2
IL-22BP	interleukin 22 binding protein
IL-22R	interleukin 22 receptor
IL-22R1	interleukin 22 receptor 1
IL4Ra	interleukin 4 receptor a
IMP	investigational medicinal product
IND	Investigational New Drug

IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	Intravenous(ly)
JAK	janus kinase inhibitor
JP	Japan
KLH	keyhole limpet hemocyanin
LEO 138559	investigational medicinal product investigated in this trial
LOCF	last observation carried forward
LS	least squares
mAb	monoclonal antibody
MAD	multiple ascending dose
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed model repeated measures
MoA	mode of action
NA	not applicable
NCT	National Clinical Trial
NOAEL	no-observed-adverse-effect level
NRI	non-responder imputation
NRS	numeric rating scale
PCR	polymerase chain reaction
PD	pharmacodynamics
PDE-4	phosphodiesterase-4
PEF	peak expiratory flow
PK	pharmacokinetics
PoC	proof of concept
POEM	Patient-Oriented Eczema Measure
PPD	purified protein derivative
PRO	patient-reported outcome
Q2W	every second week

qPCR	Quantitative polymerase chain reaction
QT	QT interval, time from start of the Q wave to the end of the T wave on an ECG tracing
RNA	ribonucleic acid
rRNA	ribosomal RNA
SAD	single ascending dose
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous(ly)
SCC	squamous cell carcinoma
SD	standard deviation
SDTM	standard data tabulation model
SOC	system organ class
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reaction
TARC	thymus and activation-regulated chemokine
TCI	topical calcineurin inhibitor(s)
TCS	topical corticosteroid(s)
Th2	T-helper 2
TMDD	target-mediated drug disposition
US	United States of America
vIGA-AD	Validated Investigator Global Assessment Scale for Atopic Dermatitis
WOCF	worst observation carried forward

1 Protocol synopsis

<table>
<tr><td>Trial ID
EudraCT no.
NCT no.
IND no.</td><td>LP0145-1376
2020-005541-16
04922021
146054</td></tr>
<tr><td>Title of trial</td><td>A phase 2a, randomised, double-blind, placebo-controlled, multi-site, proof of concept trial to evaluate the efficacy and safety of LEO 138559 in adult subjects with moderate to severe atopic dermatitis (AD).</td></tr>
<tr><td>Short title of trial</td><td>An evaluation of LEO 138559 in adults with moderate to severe atopic dermatitis.</td></tr>
<tr><td>Main objectives and endpoints</td><td>
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary objective</td><td>Primary endpoint</td></tr>
<tr><td>To compare the efficacy of LEO 138559 with placebo in subjects with moderate to severe AD.</td><td>• Change in Eczema Area and Severity Index (EASI[1]) score from baseline to Week 16.</td></tr>
<tr><td>Secondary objective</td><td>Secondary endpoints</td></tr>
<tr><td>To compare the safety of LEO 138559 with placebo in subjects with moderate to severe AD.</td><td>• Number of treatment-emergent adverse events from baseline to Week 16 per subject.</td></tr>
<tr><td colspan="2">[1] The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. The EASI is a composite index with scores ranging from 0 to 72, with higher values indicating more severe and/or more extensive condition.</td></tr>
</table>
</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:
 

[a]Screening phase of up to 4 weeks (Weeks -4 to 0) including a washout phase of 1 week (Week -1 to 0). Subjects must stop treatment with TCS, TCI, topical PDE-4 inhibitors, or other topical prescription treatments 1 week prior to randomisation. All</td></tr>
</table>

	subjects must use an emollient twice daily (or more frequently, if needed) for at least 7 days before Day 1 (baseline) and throughout the treatment period (until Week 16). [b]In addition to the Q2W dosing schedule during the treatment phase, both treatment groups will receive an additional dose of their allocated treatment (LEO 138559 450 mg or placebo) at Visit 4 (Week 1). [c]A 16-weeks safety follow-up period including 3 phone visits at Visits 13, 14, and 15 (Weeks 20, 24, and 28), and 1 safety follow-up visit at the site at Visit 16 (Week 32). **Abbreviations:** PDE-4 = phosphodiesterase-4; Q2W = every second week; TCI = topical calcineurin inhibitor(s); TCS = topical corticosteroid(s). The trial will consist of a screening period of up to 4 weeks (Weeks -4 to -0) including an applicable washout period of 1 week (Week -1 to 0), a treatment period of 16 weeks (Weeks 0 to 16), and a 16-weeks off-treatment follow-up period for the assessment of safety and anti-drug antibodies (ADA) (Weeks 16 to 32). After providing informed consent and successful completion of the screening and washout period, subjects will be randomised in a 1:1 ratio to receive LEO 138559 450 mg Q2W or placebo Q2W. Each subject will receive [redacted] SC injections (each [redacted] mL) of [redacted] mg LEO 138559 or placebo to receive a total dose of 450 mg LEO 138559 ([redacted] mL) or placebo [redacted] mL). In addition to this Q2W dosing schedule, both treatment groups will receive an additional dose of their allocated treatment (LEO 138559 450 mg or placebo) at Visit 4 (Week 1). Randomisation will be stratified by the disease severity at baseline; one stratum, 'stratum A', will be defined as having EASI <21 and the other stratum, 'stratum B', will be defined as having EASI ≥21. During the treatment period, final dosing will be administered at Week 14, regardless of AD improvement. Rescue treatment: if medically necessary (i.e., due to worsening of AD or intolerable AD symptoms), rescue treatment for AD in the form of TCS/TCI may be used from Week 4 at the discretion of the investigator. The primary endpoint will be assessed at Week 16, and the final safety assessment will be conducted at Week 32.
Main assessments	• EASI. • Treatment-emergent adverse events.
Main criteria for inclusion	• 18-64 years old (both included) at screening. • Diagnosis of AD [as defined by the AAD Consensus Criteria (1)] that has been present for ≥1 year prior to screening. • Subjects who have a recent history (within 6 months before screening) of inadequate response to treatment with topical medication, or for whom topical treatments are otherwise medically inadvisable. • EASI score ≥12 at screening and ≥16 at baseline. • vIGA-AD score ≥3 at screening and baseline. • Body surface area (BSA) of AD involvement ≥10% at screening and baseline. • Worst Daily Pruritus NRS (weekly average) of ≥3 points at baseline.
Main criteria for exclusion	• Treatment with systemic immunosuppressive/immunomodulating medication, immunoglobulin/blood products, or phototherapy within 4 weeks or 5 half-lives prior to randomisation, whichever is longer.

	• Treatment with biologics within 5 half-lives (if known) or 16 weeks prior to randomisation, whichever is longer. • Treatment with TCS, TCI, topical PDE-4 inhibitor, or other topical prescription treatments within 1 week prior to randomisation. • Treatment with a live (attenuated) vaccine within 12 weeks prior to randomisation. • Clinically significant active chronic or acute infection requiring systemic treatment within 4 weeks prior to randomisation that may compromise the safety of the subject. • Skin infection within 1 week prior to randomisation. • Presence of hepatitis B or C infection at screening. • History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening. • Subject has a positive or indeterminate test for tuberculosis at screening. • Subject is pregnant or lactating.
Investigational medicinal products	• Name of IMP: LEO 138559. • Active substance: LEO 138559, CCI mg/mL (following reconstitution). • Dosage form: Lyophilised powder for reconstitution (using 1.0 mL sterilised water) adding up to a volume of 1.2 mL/vial. • Concentration: CCI mg/mL. • Dose and frequency: 450 mg Q2W (CCI injections of CCI mg/mL). • Method of administration: Subcutaneous. • Name of IMP: Placebo. • Active substance: Placebo contains the same excipients in the same concentration as LEO 138559 only lacking the active ingredient. • Dosage form: Solution for injection (contains 1.2 mL/vial). • Concentration: Not applicable. • Dose and frequency: Not applicable and CCI injections of CCI mL placebo solution Q2W. • Method of administration: Subcutaneous.
Duration of trial participation	Up to 36 weeks
Number of subjects	A total of 52 subjects will be randomised 1:1 to: • LEO 138559 450 mg Q2W (26 subjects). • Placebo Q2W (26 subjects).
Number and distribution of trial sites	Approximately 20 sites in Canada, Germany, Poland, and the US.
Statistical methods	Primary and secondary endpoints: All subjects randomized and exposed to IMP will be included in the full analysis set (FAS) and will be analysed for the primary endpoint, based on treatment assigned. All subjects who will be exposed to IMP will be included in the safety analysis set and will be analysed for the secondary endpoint, based on actual treatment received.

	A primary and 3 supplementary estimands will be defined for the primary endpoint to ensure that occurrence of intercurrent events is taken into account. • The primary estimand for the primary endpoint will use a *hypothetical* strategy which attempts to quantify the effect of treatment, in the hypothetical situation, where one or more intercurrent events do not occur. • A first supplementary estimand will use a *composite* strategy which accounts for occurrence of pre-defined intercurrent events (initiation of rescue treatment and permanent discontinuation of IMP) as a component of the endpoint. • A second supplementary estimand will use a *pandemic-modified composite* strategy which follows a composite strategy for intercurrent events independent of the COVID-19 pandemic, attempting to quantify the effect of the randomised treatment as if the COVID-19 pandemic did not happen. • A third supplementary estimand will use a *treatment policy* strategy which attempts to quantify the effect of the randomised treatment regardless of whether an intercurrent event occurs. For the primary analysis of the primary estimand, missing data at Week 16 due to an intercurrent event will be imputed using MI (100 iterations) assuming MAR within each treatment group and whether the subject has experienced an intercurrent event. Within a given treatment group, observed data from subjects not experiencing an intercurrent event will be used to impute missing data for subjects who experience an intercurrent event. For each of the 100 complete datasets after imputation, the change in EASI score from baseline to Week 16 will be analysed using an ANCOVA model adjusted for treatment, region, baseline EASI score, and baseline disease severity. The pooled estimate of the difference in the LS-mean change from baseline, along with the associated 95% CIs and nominal p-values will be presented based on applying Rubin's rules to the estimates and standard errors from the ANCOVA analysis of the imputed datasets. The 3 supplementary estimands will be analysed using the same ANCOVA model with different imputation methods for intercurrent events. The secondary endpoint (number of treatment-emergent AEs from baseline to Week 16 per subject) will be reported descriptively by treatment group.
Signatory investigator	PPD Germany
Sponsor	LEO Pharma A/S, Industriparken 55, DK 2750 Ballerup, Denmark

2 Trial identification

EudraCT number: 2020-005541-16

NCT number: 04922021

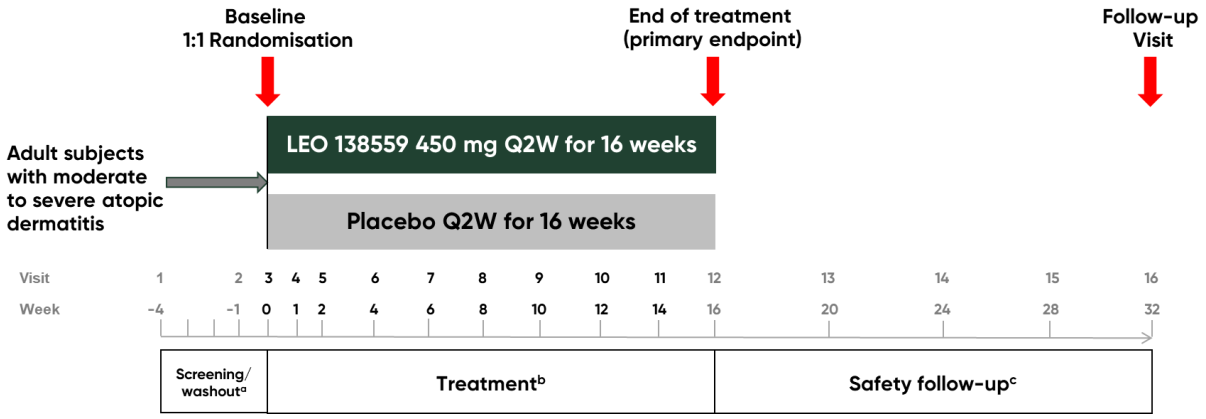
IND number: 146054

The clinical trial protocol will be registered in local registries if 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



[a]Screening phase of up to 4 weeks (Weeks -4 to 0) including a washout phase of 1 week (Week -1 to 0). Subjects must stop treatment with TCS, TCI, topical PDE-4 inhibitors, or other topical prescription treatments 1 week prior to randomisation. All subjects must use an emollient twice daily (or more frequently, if needed) for at least 7 days before Day 1 (baseline) and throughout the treatment period (until Week 16).

[b]In addition to the Q2W dosing schedule during the treatment phase, both treatment groups will receive an additional dose of their allocated treatment (LEO 138559 450 mg or placebo) at Visit 4 (Week 1).

[c]A 16-weeks safety follow-up period including 3 phone visits at Visits 13, 14, and 15 (Weeks 20, 24, and 28), and 1 safety follow-up visit at the site at Visit 16 (Week 32).

Abbreviations: PDE-4 = phosphodiesterase-4; Q2W = every second week; TCI = topical calcineurin inhibitor(s); TCS = topical corticosteroid(s).

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

	Screening[a]	Washout[a]	Baseline/ Start of treatment	Treatment								End of treatment[b] Primary endpoint[c]	SFU phone calls	SFU site visit[d]	Early IMP termination, if applicable[e]	Unscheduled. Visit[f]	References (Section in protocol)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)[g]	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Trial population and eligibility																	
Informed consent[h]	X																Appendix 3B
Subjects eligibility	X		X														8.2 and 8.3
Investigator assessments at screening and/or baseline only																	
Demographics[i]	X		X														11.2.1
Body assessment (height)	X																11.2.2
Medical history[j]	X		X														11.2.3

	Screening[a]	Washout[a]	Baseline/ Start of treatment	Treatment								End of treatment[b] Primary endpoint[c]	SFU phone calls	SFU site visit[d]	Early IMP termination, if applicable[e]	Unscheduled. Visit[f]	References (Section in protocol)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)[g]	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Hepatitis B, C, HIV	X																11.2.4 and Exclusion criterion no. 14 and 15
Tuberculosis (*Mycobacterium tuberculosis* IFN-γ release assay)[k]	X																11.2.4 and Exclusion criterion no. 16
Serum pregnancy test (females only)[l]	X																11.4.5 and Inclusion criterion no. 10

	Screening[a]	Washout[a]	Baseline/ Start of treatment	Treatment								End of treatment[b] Primary endpoint[c]	SFU phone calls	SFU site visit[d]	Early IMP termination, if applicable[e]	Unscheduled. Visit[f]	References (Section in protocol)
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Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)[g]	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
SARS-CoV-2 PCR test	X																11.2.4, 11.4.5, and exclusion criterion no. 30
Randomisation and treatments																	
Randomisation			X														9.3
IMP administration at the trial site			X	X[m]	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)	9.8.4
Drug accountability			X	X	X	X	X	X	X	X	X					(X)	9.8.3

	Screening[a]	Washout[a]	Baseline/ Start of treatment	Treatment								End of treatment[b] Primary endpoint[c]	SFU phone calls	SFU site visit[d]	Early IMP termination, if applicable[e]	Unscheduled. Visit[f]	References (Section in protocol)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)[g]	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Background treatment (emollients)[n]		At least twice daily															9.4
Concomitant medications/ concurrent procedures[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	9.6
Subject assessments (eDiary)																	
eDiary hand-out / training		X															
Return of eDiary[p]														X	(X)		

	Screening[a]	Washout[a]	Baseline/ Start of treatment	Treatment								End of treatment[b] Primary endpoint[c]	SFU phone calls	SFU site visit[d]	Early IMP termination, if applicable[e]	Unscheduled. Visit[f]	References (Section in protocol)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)[g]	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Investigator assessments of efficacy																	
EASI	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)	11.3.2
BSA involvement	X		X	X	X	X	X	X		X		X		X	(X)	(X)	11.3.3
Subject assessments of efficacy and HRQoL																	
Worst Daily Pruritus NRS[q]		Daily															11.3.4.2
POEM[r]			X	X	X	X	X	X		X		X			(X)	(X)	11.3.4.3
DLQI[r]			X	X	X	X	X	X		X		X			(X)	(X)	11.3.4.4

	Screening[a)]	Washout[a)]	Baseline/ Start of treatment	Treatment								End of treatment[b)] Primary endpoint[c)]	SFU phone calls	SFU site visit[d)]	Early IMP termination, if applicable[e)]	Unscheduled. Visit[f)]	References (Section in protocol)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)[g)]	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Investigator assessments of safety																	
Vital signs[s)]	X		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)	(X)	11.4.2
Weight	X											X		X	(X)	(X)	11.4.3
ECG[t)]	X		X			X		X		X		X		X	(X)	(X)	11.4.4
Clinical chemistry, haematology (central laboratory)	X		X		X	X		X		X		X		X	(X)	(X)	11.4.5
IgE			X			X						X		X	(X)	(X)	11.4.5
Urinalysis[u)]	X		X			X		X		X		X		X	(X)	(X)	11.4.5

	Screening[a]	Washout[a]	Baseline/ Start of treatment	Treatment								End of treatment[b] Primary endpoint[c]	SFU phone calls	SFU site visit[d]	Early IMP termination, if applicable[e]	Unscheduled. Visit[f]	References (Section in protocol)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)[g]	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Urine pregnancy test (females only)[i]			X			X		X		X		X		X	(X)	(X)	11.4.5
ADA			X			X		X		X		X		X	(X)	(X)	11.4.6
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	13
Pharmacokinetic assessment																	
PK blood samples			X	X	X	X	X	X	X	X	X	X		X	(X)	(X)	11.5
Pharmacodynamic assessments																	
Blood biomarkers (PD serum sample)			X		X	X		X				X			(X)	(X)	11.6.2
Skin swabs			X									X			(X)	(X)	11.6.3
Tape strips			X									X			(X)	(X)	11.6.4

	Screening[a]	Washout[a]	Baseline/ Start of treatment	Treatment								End of treatment[b] Primary endpoint[c]	SFU phone calls	SFU site visit[d]	Early IMP termination, if applicable[e]	Unscheduled. Visit[f]	References (Section in protocol)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)[g]	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
End of treatment/trial																	
End-of-treatment form												X			X		11.7
End-of-trial form														X	X		11.7

a) Screening will be performed up to 4 weeks before the baseline visit and can be combined with the washout visit (Visit 2) if needed.

b) An end-of-treatment form must be completed in the eCRF for all randomised subjects. See Section 11.7 for further details.

c) Subjects who permanently discontinue IMP treatment prior to Week 16 will be asked to return to the trial site at Week 16 for a primary endpoint (nominal Week 16) visit.

d) An end-of-trial form must be completed in the eCRF for all randomised subjects. See Section 11.7 for further details.

e) 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 and will be followed up as described in Section 10.3. As an early termination visit will only be performed in case of subjects permanently discontinuing the IMP, the visit has been marked with an (X).

f) Unscheduled visit(s) between planned visits may be added to the subject's visit schedule if judged necessary by the investigator, e.g., due to an AE, a significant change in disease state, or difficulty complying with the clinical trial protocol requirements. At an unscheduled visit, the investigator should at least collect AEs data. Other assessments/procedures to be conducted at an unscheduled visit will be at the discretion of the investigator. As unscheduled visits will only be performed if judged necessary by the investigator, the visits have been marked with an (X).
g) If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to randomisation/baseline.
h) The informed consent form must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations and washout of disallowed medications.
i) At screening, the demographic data listed in Section 11.2.1 will be recorded. At baseline, only age will be recorded.
j) In case medical history is incomplete at the screening visit, missing data will be retrieved at Week 0 (baseline).
k) *Mycobacterium tuberculosis* IFN-γ release assay (or a PPD test if it is a requirement from the local health authorities).
l) For women of childbearing potential (as defined in inclusion criterion no. 10 and 11, Section 8.2).
m) In addition to the Q2W dosing schedule, both treatment groups will receive an additional dose of LEO 138559 450 mg or placebo at Week 1.
n) All subjects must use an emollient twice daily (or more frequently, if needed) for at least 7 days before Day 1 (baseline) and throughout the treatment period (until Week 16).
o) Relevant concomitant medications/ concurrent procedures should be included from 3 months prior to screening until end of trial (Week 32).
p) At Week 32, subjects will be asked to bring the eDiary back to the clinic.
q) Completion of the eDiary for Worst Daily Pruritus NRS will be initiated at least 1 week prior to baseline (Day 1). Compliance with the eDiary completion will be reviewed by the trial site staff throughout the trial. Subjects who discontinue IMP but remain in the trial will continue completing the eDiary until the safety follow-up visit (Visit 16).
r) At the screening visit (at the earliest Week -4), the subject's eligibility to participate in the trial must be confirmed before any PROs are completed. PROs will be collected in the electronic device at the trial site and should be completed before the investigator's assessment of efficacy.
s) For the first 3 IMP treatment visits (i.e., Visits 3, 4, and 5) subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 1 hour with vital signs taken immediately after IMP administration as well as after 30 minutes (± 5 minutes) and after 1 hour (± 5 minutes), or until stable, whichever is later.

t) ECG should be recorded in triplicate for each time point and will be centrally evaluated.

u) Urinalysis is performed by a urine dipstick. The analytes listed in Section 11.4.5 will only be measured if the urine dipstick is abnormal.

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eCRF = electronic case report form; HIV = human immunodeficiency virus; HRQoL = health related quality of life; IFN-γ = interferon gamma; IgE = immunoglobulin E; IMP = investigational medicinal product; NRS = Numeric Rating Scale; PCR = polymerase chain reaction; PD = pharmacodynamics; PK = pharmacokinetics; POEM = Patient-Oriented Eczema Measure; PPD = purified protein derivative; PRO = patient-reported outcome; Q2W = every second week; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SFU = safety follow-up; vIGA-AD = validated Investigator Global Assessment Scale for Atopic Dermatitis.

5 Introduction and trial rationale

5.1 Atopic dermatitis

AD is a chronic inflammatory disease characterised by recurrent, erythematous, and xerotic lesions with exudation at acute stages and fissuring and lichenification at chronic stages. The clinical course of AD typically follows a chronic, relapsing-remitting pattern with periods of worsening ('flares'). AD lesions are accompanied by intense pruritus and sometimes pain leading to poor quality of life, sleep deprivation, mood changes, and lost productivity (2-4). AD is the most common inflammatory skin disorder with a lifetime prevalence of 15–20% (5). While AD was initially thought to be a disease of early childhood, more recent evidence demonstrates adult annual prevalence rates up to 10%, and 1 in 4 adults with AD report adult-onset disease (6, 7).

AD is a heterogenous disease mediated by varying degrees of epidermal barrier disruption, immune cell activation, and microbiome dysbiosis. Epidermal barrier disruption leads keratinocytes to express chemokines and cytokines that activate antigen presenting cells (APCs) and recruit Th2 cells and innate lymphoid cells (8, 9). These cells amplify the type 2 immune response by secreting IL-4, IL-5, and IL-13 (10-12). As AD progresses from acute to chronic, a mixed T-cell infiltrate including Th17 and Th22 cells develops (13). These cells secrete IL-17 and IL-22, which have been purported to play a role in AD pathogenesis (14, 15). Whether IL-22 is a key driver of AD pathogenesis remains unknown.

Topical therapies are the mainstay of treatment for AD and include moisturisers, TCS, TCI, and PDE-4 inhibitors (16). In addition, topical JAK inhibitors (cream) are in development for the treatment of AD (17, 18) and the topical JAK inhibitor delgocitinib (ointment) has received marketing approval in Japan (19). If disease control cannot be achieved with topical treatments, phototherapy can be considered (20). For patients with moderate to severe AD, topical therapy and phototherapy are often insufficient or impractical, and therefore systemic therapy is indicated. Systemic non-biologic therapies include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. Cyclosporine is approved for the treatment of severe AD in multiple European countries and Japan. However, its use is limited by the risk of nephrotoxicity and therefore long-term therapy (>1-2 years) is not recommended. In addition, azathioprine, methotrexate, and mycophenolate mofetil have demonstrated varying levels of efficacy (21, 22) and are used off-label. In 2017, the first biologic was approved for the treatment of moderate to severe AD (dupilumab, anti-IL4Ra mAb) and there are several targeted biologic therapies in development for AD including tralokinumab, lebrikizumab, and nemolizumab (23-25), as well as oral JAK inhibitors (26-28) . Of note, baricitinib was

recently approved by the EMA for the treatment of moderate to severe AD (29), however, its position in the treatment paradigm is not yet fully understood (30).

Despite promising efficacy with dupilumab, approximately 60% of patients with AD do not achieve clinical remission (i.e., IGA 0/1, clear/almost clear). Therefore, there is a remaining unmet need to develop new therapies with improved efficacy. Further, it is increasingly recognised that AD is a phenotypically and molecularly heterogenous disease that may require differentiated and/or combined therapeutic approaches in order to adequately address the needs of moderate to severe AD patients (31, 32).

5.2 Experience with investigational medicinal product

Nonclinical data

LEO 138559, originally known as ARGX-112 (clone CCI), is a humanised IgG1 mAb with high affinity for the IL-22R1 chain of the IL-22R, thereby blocking the binding of the ligand, dimerisation of IL-22R1 with IL-10R2, and downstream signalling via JAK1-STAT3 (33). Given the binding of LEO 138559 to IL-22R1, it is hypothesised to prevent not only the effects of IL-22 but also partially CCI and CCI . Further, LEO 138559 does not bind to IL-22BP, an endogenous negative regulator of IL-22, and thereby leaves IL-22BP free to further inhibit IL-22 cellular activity (34). Therefore, LEO 138559 is considered an optimal therapeutic tool to inhibit the IL-22 pathway.

LEO 138559 has been modified to avoid Fc effector functions (binding of its Fc region to Fc receptors on e.g., effector cells) that can induce unwanted effects of the IMP. It is expected that LEO 138559 Q2W will offer an acceptable safety profile in combination with an efficacious treatment option for the benefit of patients with moderate to severe AD.

Toxicology

The LEO 138559 nonclinical studies conducted to date (4- and 26-week repeat dose toxicology studies in cynomolgus monkeys with 5 weekly SC or IV doses up to 100 mg/kg) showed no signs of local or systemic toxicities in nonhuman primates (cynomolgus monkeys).

The LEO 138559 nonclinical data indicated a toxicity profile that is amenable to clinical monitoring, is of low concern for human risk, and provides an approximate CCI -fold margin of exposure between the observed NOAELs and the exposure at steady state for 450 mg Q2W dosing (planned dosing regimen in LP0145-1376).

As expected for a mAb drug, the nonclinical results did not indicate a need to perform specific clinical trials (typically conducted for small molecule drugs) investigating effects on

QT prolongation, implication of hepatic or renal impairment and, cytochrome P450 induction/inhibition potential.

Based on nonclinical pharmacology and toxicology studies, LEO 138559 is expected to be a safe and efficacious treatment for the benefit of patients with moderate to severe AD.

From the MoA, target expression, class effects of other biologics, and literature review, potential risks have been identified which are included in the investigator's brochure (Section 7.3.2) (35).

A detailed overview of nonclinical data on LEO 138559 is available in the current investigator's brochure (35).

Clinical data

LEO 138559 is in early development with 1 ongoing first-in-human clinical trial: LP0145-1315. This is a phase 1, randomised, double-blind, placebo-controlled, multi-centre, SAD, and MAD trial to evaluate the safety, tolerability, PK, and PD of LEO 138559 in healthy volunteers and subjects with moderate to severe AD. The trial consists of 2 parts: SAD and MAD.

To date in the LP0145-1315 trial, single IV doses up to CCI mg LEO 138559 or placebo and single SC doses up to CCI mg LEO 138559 or placebo have been administered to healthy subjects. LEO 138559 or placebo are administered SC as once-weekly doses in healthy subjects (CCI mg) and in AD patients (CCI and CCI mg) for 5 weeks. In AD patients, a reduction in disease severity based on individual EASI scores was observed for LEO 138559 compared with placebo. No SAEs and no AE patterns giving rise to any concerns have been reported. No risks for humans have been identified at the dose levels tested to date.

Prior to LP0145-1315, there was no clinical experience of administering of LEO 138559 to humans. However, the anti-IL-22 mAb fezakinumab (ILV-094, Pfizer) was well tolerated when IV administered to AD patients and improved disease scores in patients with severe AD after 12 weeks in a phase 2a trial (36). Fezakinumab was also well tolerated in a safety and efficacy trial where it was administered SC in rheumatoid arthritis patients on a stable background of methotrexate (37).

Pharmacokinetics

Based on the preliminary human PK data, the PK of LEO 138559 is as expected for a mAb directed toward a membrane-bound target, and the TMDD characteristics are also visible in the observed human data as it was in the cynomolgus data.

After SC administration, LEO 138559 is slowly absorbed with a mean time to maximum concentration of approximately CCI days. After multiple dosing, the elimination half-life was observed to be between CCI days. At and above the exposure level relevant for clinical testing (CCI mg Q2W), the elimination is dominated by linear clearance and close to dose-proportionality is expected at steady state. The exposure at steady state following administration of 450 mg Q2W is expected to result in lower exposure than 450 mg every week for 5 weeks (the CCI in the LP0145-1315 trial).

A detailed overview of clinical data on LEO 138559 is available in the current investigator's brochure (35).

5.3 Trial rationale

There remains an unmet need for effective treatment options in patients with moderate to severe AD. Building on the knowledge of excessive IL-22 expression in AD, we hypothesise that inhibition of the IL-22 pathway via LEO 138559 may be an effective treatment in patients with moderate to severe AD. The primary goal of the PoC trial will be to evaluate whether patients with moderate to severe AD who are treated with LEO 138559 demonstrate improved efficacy compared with placebo.

5.4 Ethical considerations

This trial will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki (38) and ICH GCP (39) 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 138559 will be evaluated in adults with moderate to severe AD who may benefit from treatment with LEO 138559. Appropriate measures will be taken to protect the subject from potential risks related to treatment with LEO 138559 and to closely monitor the subject as explained in Section 5.5 below.

Participation in the trial is voluntary and the subject can 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 not be included in the trial. Women of childbearing potential must agree to use a highly

effective form of contraception to prevent pregnancy during the trial. In addition, pregnancy tests 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 not be included in the trial.

In accordance with the current version of ICH and GCP guidelines, qualified medical personnel employed by LEO Pharma will readily be available to advise on trial-related medical questions. Medical monitoring will be conducted throughout 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. As a novel IL-22R antagonist, LEO 138559 is expected to be efficacious against AD.

Risks to subjects in the trial will be minimised by inclusion of subjects fulfilling all eligibility criteria (Sections 8.1 to 8.3) and by close clinical monitoring (Section 4). Discontinuation and withdrawal criteria are also in place (Section 10.2).

The subject will be informed that changes to their ongoing AD treatment may be required during the screening period up to Visit 6 (Week 4) and that their condition may worsen as a result. To minimise the negative consequences of this for the subject and ensure subject safety, investigators will be asked only to include subjects who are considered able to discontinue prohibited medications during the screening period without experiencing intolerable worsening of AD.

The subject will also be informed of the possibility and probability of receiving active or placebo treatment. In this trial, approximately 50% of the subjects will receive active treatment with LEO 138559. A benefit for all subjects participating in this trial regardless of whether they receive active drug or placebo is that they receive close monitoring of their disease and easy access to specialist care.

After randomisation and if medically necessary (i.e., due to worsening of AD or intolerable worsening of AD symptoms), rescue treatment of AD may be provided to the subject after Week 4 at the discretion of the investigator. All subjects may receive rescue treatment, regardless of treatment allocation (Section 9.5). The subject will be instructed to inform the investigator if their AD significantly worsens at any time during the trial.

Blood sampling presents the same low risk as normally associated with this procedure (i.e. infection, bleeding into the surrounding tissue, and, very rarely, inflammation of the vein, or formation of blood clots). Blood sampling will only be conducted by qualified medical personnel. Collection of tape strips and skin swabs are non-invasive techniques with no or very limited risks to the subject.

LEO Pharma has evaluated currently available safety data on LEO 138559. IL-22R is expressed on epithelial cells and not on immune cells. IL-22 has shown to be involved in the production of antimicrobial peptides in the skin, lung, and intestines. Therefore, when blocking the IL-22 receptor, there is a potential for reduced antimicrobial peptide production and consequently a theoretically increased risk of infection. However, based on nonclinical studies, LEO 138559 is considered immunomodulatory, and not immunosuppressive. Regarding the ability to mount effective antibody immune responses, an assessment of the effect of LEO 138559 on the immune response was performed in an immune-toxicological study in monkeys. The study concluded that KLH-specific antibody responses (IgG and IgM) to the first and second immunisations with KLH occurred in all animals. Importantly, no adverse effect on the ability to mount a humoral primary or memory response was noted in animals administered up to 100 mg/kg LEO 138559. Further, no indicators of immunosuppression (e.g., haematological changes, organ weights, infections, and histology) were observed in 4- and 26-week nonclinical toxicology studies.

Participation in any clinical trial is currently associated with increased risk and added challenges due to the COVID-19 pandemic caused by SARS-CoV-2. The proposed trial and treatment with LEO 138559 are not believed to put subjects with AD under an increased risk for viral infections including SARS-CoV-2. However, the risk of exposure to infected people cannot be excluded as the trial subjects may need to expose themselves to public areas (e.g., commute to the trial site) and have additional human contact (e.g., with trial site staff). Both EMA (40) and FDA (41) as well as national health authorities in Europe have issued guidelines aiming at providing recommendations for conducting clinical trials during the COVID-19 pandemic. Given the rapidly evolving epidemic situation and the potential for the pandemic to relapse in the future, LEO Pharma will carefully monitor the pandemic situation and issue risk mitigation measures to protect subjects and staff involved in the trial against infection with SARS-CoV-2 and to ensure integrity of the trial data (Appendix 9). A number of eligibility criteria have been added to reduce the risk of severe SARS-CoV-2 infections (Sections 8.1 to 8.3).

During the trial, the investigators will be trusted to take appropriate action to ensure individual subject safety according to the recommendations and preventive measures issued

by their local authorities. As these can differ across countries and regions, no general instructions from the sponsor can be provided in relation to subject safety and the need for postponing/cancelling visits during the trial.

However, safety monitoring is an obligation of LEO Pharma and in case the subject, due to local restrictions, is prevented from coming to the trial site, the investigator can convert on-site visits into phone visits for the purpose of safety monitoring (for details refer to Appendix 9). The phone visits must, however, not be used for the investigator's assessments of efficacy. Other mitigation measures include POEM and DLQI collected on the web-based solution by remote transfer to the vendor (see Appendix 3D).

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 SC treatment option for AD. The current benefit-risk profile is therefore deemed in favour of conducting the present trial.

6 Trial objectives and endpoints

Trial objectives and endpoints are presented in Panel 3. 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 3: Objectives and endpoints

Objectives	Endpoints
Primary objective	
To compare the efficacy of LEO 138559 with placebo in subjects with moderate to severe AD.	*Primary endpoint* • Change in Eczema Area and Severity Index (EASI) score from baseline to Week 16. *Exploratory endpoints (efficacy)* • 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 score of 0 (clear) or 1 (almost clear) at Week 16. • Time to having a decrease in EASI of at least 50% (EASI 50) between baseline and Week 16. • Time to having a decrease in EASI of at least 75% (EASI 75) between baseline and Week 16. • Time to having a decrease in EASI of at least 90% (EASI 90) between baseline and Week 16. • Time to initiation of TCI or TCS rescue treatment between baseline and Week 16. *Exploratory endpoints (patient-reported outcomes)* • Change in Worst Daily Pruritus NRS (weekly average) from baseline to Weeks 1, 2, 4, 8, 12, and 16. • Having a decrease in Worst Daily Pruritus NRS (weekly average) of ≥3 points from baseline at Weeks 1, 2, 4, 8, 12, and 16, assessed separately. • Time to reduction of Worst Daily Pruritus NRS (weekly average) of ≥3 points between baseline and Week 16. • Having a decrease in Worst Daily Pruritus NRS (weekly average) of ≥4 points from baseline at

Objectives	Endpoints
	Weeks 1, 2, 4, 8, 12, and 16, assessed separately, among subjects with a baseline Worst Daily Pruritus NRS ≥4 points. • Time to reduction of Worst Daily Pruritus NRS (weekly average) of ≥4 points between baseline and Week 16 among subjects with a baseline Worst Daily Pruritus NRS ≥4 points. • Change in POEM score from baseline to Week 16. • Change in DLQI from baseline to Week 16.
Secondary objective	
To compare the safety of LEO 138559 with placebo in subjects with moderate to severe AD.	*Secondary endpoint* • Number of treatment-emergent adverse events from baseline to Week 16 per subject. *Exploratory endpoint (ADA)* • Having a positive ADA response at Weeks 0, 4, 8, 12, 16, 32, assessed separately.
Exploratory objectives	
To evaluate the pharmacokinetics of LEO 138559 for 16 weeks in subjects with moderate to severe AD	*Exploratory endpoint (pharmacokinetics)* • Serum concentration of LEO 138559 at Weeks 0, 1, 2, 4, 6, 8, 10, 12, 14, 16, 32, assessed separately.
To evaluate the effect of treatment with LEO 138559 compared with placebo for 16 weeks on disease biomarkers in subjects with moderate to severe AD	*Exploratory endpoints (pharmacodynamics)* • Change in expression of AD disease biomarkers in serum from baseline to Week 16. • Change in expression of AD disease biomarkers in skin from baseline to Week 16.

Abbreviations: AD = atopic dermatitis; ADA = anti-drug antibodies; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI 50 = at least 50% decrease in EASI score; EASI 75 = at least 75% decrease in EASI score; EASI 90 = at least 90% decrease in EASI score; NRS = numeric rating scale; POEM = Patient-Oriented Eczema

Measure; TCI = topical calcineurin inhibitor(s); TCS = topical corticosteroid(s); vIGA-AD = Validated Investigator Global Assessment Scale for Atopic Dermatitis.

7 Trial design

7.1 Overall trial design

Overview
This is a phase 2a, randomised, double-blind, placebo-controlled, multi-site, proof of concept trial to evaluate the efficacy and safety of SC administered LEO 138559 in adult subjects with moderate to severe AD. A schematic overview of the trial design is presented in Panel 1.

The trial will consist of:

- A screening period of up to 4 weeks (Weeks -4 to 0) including an applicable washout period of 1 week (Week -1 to 0).
- A treatment period of 16 weeks (Weeks 0 to 16).
- A follow-up period of 16 weeks (Weeks 16 to 32) for the assessment of safety and ADA.

Randomisation will take place at Week 0. The primary endpoint will be assessed at Week 16. The final safety assessments will be conducted at Week 32 (end of trial).

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

Screening period (between 0 and 4 weeks prior to the baseline visit [Day 1])
In the screening period, eligibility of the subject (Sections 8.1 to 8.3) to participate in the trial will be evaluated at a screening visit (Visit 1). This visit will be performed up to 4 weeks before the baseline visit (Visit 3) and can be combined with the washout visit (Visit 2) if needed.

At the washout visit (Visit 2, Week -1), subjects will stop any treatment with TCS, TCI, PDE-4 inhibitors, or other topical prescription treatments, and start application of an emollient to all affected areas of the skin twice daily (or more frequently, if needed). The daily application of the emollient should continue throughout the treatment period. Moreover, at the washout visit (Visit 2), the subjects will receive training in completion of an eDiary and will be given an electronic device to record the Worst Daily Pruritus NRS. To complete training of the eDiary, and as an opportunity to fill out Worst Daily Pruritus NRS before the treatment period, subjects will be asked to complete Worst Daily Pruritus NRS at the visit. Completion of the eDiary will be initiated at the latest 1 week prior to the baseline visit (Visit 3, Week 0).

Randomisation (Week 0)
At baseline (Visit 3, Week 0), eligible subjects will be randomised 1:1 to 1 of 2 treatment groups: LEO 138559 or placebo. Randomisation will be stratified by baseline disease severity. One stratum, 'stratum A', will be defined as having EASI <21 and the other stratum, 'stratum B', will be defined as having EASI ≥21. IRT will be used to control randomisation and stratification factors.

Treatment period (Week 0 to Week 16)
In the treatment period, LEO 138559 or placebo injections will be administered at the site by site staff Q2W for 16 weeks (Section 9.2). In addition to this Q2W dosing schedule, both treatment groups will receive an additional dose of their allocated treatment (LEO 138559 450 mg or placebo) at Visit 4 (Week 1). During the treatment period, the subject will be asked to continue applying the emollient twice daily (or more frequently, if needed). The subject will also be asked to visit the clinic for assessments and procedures. Final dosing will be administered at Week 14, regardless of AD improvement. If medically necessary (i.e. due to worsening of AD or intolerable AD symptoms), rescue treatment for AD in the form of TCS/TCI may be used from Week 4 at the discretion of the investigator.

Safety follow-up period (Week 16 to Week 32)
In the safety follow-up period, the subject will stop treatment with LEO 138559 or placebo injections and the safety of the subject will further be assessed at 3 safety follow-up phone calls (Weeks 20, 24, and 28) and at a final safety follow-up visit at Week 32. Topical treatment for AD will be permissible during the safety follow-up period.

7.2 Number of subjects needed

Based on an anticipated screening failure rate of 35%, the planned number of subjects to screen is set to 80.

At Week 0 (baseline), a total of 52 subjects will be randomised 1:1 to:

- LEO 138559 450 mg (26 subjects).
- Placebo (26 subjects).

Based on an anticipated attrition rate of 30% in both treatment groups, this will provide a total of 36 subjects for analysis (18 subjects per treatment group).

The trial will be conducted at approximately 20 sites in Canada, Germany, Poland, and the US.

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

7.3 End-of-trial definition

A subject is considered to have completed the trial if they have completed all periods of the trial including the safety follow-up visit at Week 32 (see Section 11.7 for data to be recorded on the end-of-trial form).

The end of the trial is defined as the date of the last safety follow-up visit (Week 32) for 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.

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 at visits specified in Section 4. It will be recorded in the eCRF if the subject has met all the inclusion criteria and none of the exclusion criteria.

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

8.2 Inclusion criteria

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

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures.

2. 18-64 years old (both included) at screening.

3. Diagnosis of AD [as defined by the AAD Consensus Criteria (1) and Appendix 4] that has been present for ≥1 year prior to screening.

4. Subjects who have a recent history (within 6 months before screening) of inadequate response to treatment with topical medication, or for whom topical treatments are otherwise medically inadvisable.

    - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to higher potency (±TCI as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super potent TCS), whichever is shorter.
    - Subjects with documented systemic treatment or phototherapy for AD in the past 6 months are considered as inadequate responders to topical treatment and are potentially eligible for trial inclusion after appropriate washout.

- Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the subject's treating physician.

5. EASI score ≥12 at screening and ≥16 at baseline.

6. vIGA-AD score ≥3 at screening and baseline.

7. Body surface area (BSA) of AD involvement ≥10% at screening and baseline.

8. Worst Daily Pruritus NRS (weekly average) of ≥3 points at baseline.
   NOTE: The baseline weekly average will be calculated from daily assessments of itch severity during the 7 days immediately preceding randomisation. A minimum of 4 daily itch scores out of the 7 days is required to calculate the baseline average score. For subjects who do not have at least 4 daily itch scores reported during the 7 days immediately preceding the planned randomisation date, randomisation can be postponed until the requirement of 4 daily entries is met, but without exceeding the 28-day maximum duration for screening.

9. Subject agrees to apply an emollient twice daily (or more frequently, if needed) to AD lesional and non-lesional skin for at least 7 days before baseline.

10. A woman of childbearing potential* must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline.

11. A woman of childbearing potential* must use a highly effective** form of birth control throughout the trial and at least for 18 weeks after last administration of IMP.

    * A woman of childbearing potential is defined as a female subject aged ≥12 years old *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 cause prior to screening), or surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

**A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year) such as bilateral tubal occlusion, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), sexual abstinence (when this is in line with the preferred and usual life style of the subject and not just being without a current partner), same-sex partner, or vasectomised partner (given that the subject is monogamous).

8.3 Exclusion criteria

Subjects must not enter the trial if they fulfil any of the following exclusion criteria:

1. Active dermatologic condition that could confound the diagnosis of AD or interfere with assessment of the treatment.
2. Previously randomised in this clinical trial.
3. Current participation in any other interventional clinical trial.
4. Treatment with systemic immunosuppressive/immunomodulating medication, immunoglobulin/blood products, or phototherapy within 4 weeks or 5 half-lives prior to randomisation, whichever is longer.
5. Treatment with biologics within 5 half-lives (if known) or 16 weeks prior to randomisation, whichever is longer.
6. Treatment with TCS, TCI, topical PDE-4 inhibitor, or other topical prescription treatments within 1 week prior to randomisation.
   NOTE: Subject may be rescreened (once) if failed for this criterion (see Section 8.4).
7. Treatment with a live (attenuated) vaccine within 12 weeks prior to randomisation.
8. History of malignancy within 5 years prior to randomisation, apart from nonmetastatic basal cell carcinoma, squamous cell carcinoma of the skin, or cervical carcinoma in-situ, considered cured by the standard of care.
9. Clinically significant active chronic or acute infection requiring systemic treatment within 4 weeks prior to randomisation that may compromise the safety of the subject.
   NOTE: Subject may be rescreened (once) after infection resolves (see Section 8.4).
10. Skin infection within 1 week prior to randomisation.
    NOTE: Subject may be rescreened (once) after infection resolves (see Section 8.4).

11. Current or recent (within 2 years prior to randomisation) gastrointestinal ulcers.
12. History of any of the following: anaphylaxis, immune complex disease, pancreatic disease, inflammatory bowel disease, or known or suspected history of immunosuppressive disorder.
13. Known or suspected hypersensitivity to any component(s) of the IMP.
14. Presence of hepatitis B or C infection at screening. These are defined as: 1) Positive hepatitis C Ab, or 2) Positive HBsAg, or 3) Negative anti-HBs Ab AND positive anti-HBc Ab.
15. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.
16. Subject has a positive or indeterminate *Mycobacterium tuberculosis* IFN-γ release assay test or a positive purified protein derivative (PPD) test at screening.
    NOTE: The PPD test is only accepted if it is a requirement from local health authorities.
17. Current diagnosis of diabetes.
18. Serious heart conditions (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and/or pulmonary hypertension).
19. Chronic lung diseases (e.g., chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and/or cystic fibrosis).
20. Moderate to severe asthma [as defined by GINA guidelines (42)].
21. Obesity (BMI ≥35).
22. Subject has laboratory abnormalities that, in the opinion of the investigator, will prevent the subject from completing the trial or interfere with the analysis of results.
23. Subject is pregnant or lactating.
24. Subject has a history of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
25. Employees of the trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.

26. Any disorder* at screening and/or baseline, which is not stable in the opinion of the investigator, and could:
    a. Affect the safety of the subject throughout the trial.
    b. Influence the findings of the trial.
    c. 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.
27. Any significant abnormal finding* at baseline and/or screening which may in the opinion of the investigator:
    a. Put the subject at risk because of their participation in the trial.
    b. Influence the results of the trial.
    c. Influence the subject's ability to complete the trial.

    *Examples include clinically significant abnormal vital sign, physical examination, ECG, and laboratory result.
28. Treatment with any non-marketed drug substance (that is, an agent which has not yet been made available for clinical use following registration) within the last 4 weeks or 5 half-lives prior to randomisation, whichever is longer.
29. Subjects who are legally institutionalised.
30. Positive SARS-CoV-2 PCR test at screening.
    NOTE: Subject may be rescreened (once) if failed for this criterion (see Section 8.4).

8.4 Screening and screening failures

Subject identification number

Trial participation begins once written informed consent is obtained (refer to Appendix 3B for details on the informed consent process). Once informed consent is obtained, a 10-digit subject identification number (subject ID xxxx-xxxx-xx) will be assigned by a central IRT system. The date of first screening activity could be on the same day or a later date than the informed consent was signed. The subject ID will be used to identify the subject during the screening process and throughout trial participation, if applicable. Subjects who have given written informed consent to participate in the trial and who have been assigned a subject ID are considered 'screened' subjects.

Investigator logs

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

Screening failures

Screen failures are defined as subjects who consent to participate in the trial but are not subsequently randomly assigned to trial treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the CONSORT publishing requirements (43) and to respond to queries from regulatory authorities. As a minimum, the following data will be collected in the eCRF for screen failures:

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

Any SAE will require expedited reporting as described in Section 13.7.

Rescreening of screening failures (subjects who did not meet the eligibility criteria for participation in the trial) is not allowed except in specific situations as described below.

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), rescreening may be permitted. In addition, rescreening may be permitted (once) if an infection resolves after initially not having met exclusion criteria no. 9 (active chronic or acute infection requiring systemic treatment), no. 10 (skin infection), or no. 30 (positive SARS-CoV-2 PCR test) or if the subject failed exclusion criterion no. 6 (treatment with TCS, TCI, or topical PDE-4 inhibitor, or other topical prescription treatments). Rescreening will require approval by the sponsor's medical expert after thorough review of eCRF data from the first screening visit. In all cases, rescreening will only be permitted if the duration of the screening period does not exceed 28 consecutive days in total. Subjects to be rescreened must sign a new ICF. Rescreened 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 product description

LEO 138559 is a human recombinant mAb of the IgG1 subclass that specifically binds to human IL-22R1 and inhibits the ligand IL-22 from binding to it. It is presented as a lyophilised powder for reconstitution (using 1.0 mL sterilised water) and injection.

LEO 138559 and placebo will be packaged in individually numbered kits. Refer to Panel 4 for further details.

Panel 4: Identification of investigational medicinal products

Investigational medicinal product	Dosage form	Volume to be SC injected	Active ingredient and concentration	Pack size	Source
LEO 138559	Lyophilised powder for reconstitution (using 1.0 mL sterilised water) adding up to a volume of 1.2 mL/vial	CCI (CCI vials of CCI mL each)	LEO 138559, CCI mg/mL (following reconstitution)	CCI mg/vial	LEO Pharma
Placebo	Solution for SC injection (contains 1.2 mL/vial)	CCI mL (CCI vials of CCI mL each)	Not applicable	1.2 mL/vial	LEO Pharma

Note: To ensure that 1.0 mL can be withdrawn by a syringe, there will be a small overfill in the placebo vial and in the active IMP vial after reconstitution, of approximately 0.2 mL per vial.

Abbreviation: SC = subcutaneous(ly).

No active comparators will be used in this trial.

9.2 Administration of 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. The IRT system will assign the required kit number(s) for each subject at each dispensing visit.

The first day of dosing is considered Day 1 (Week 0). Each subject will receive [redacted] SC injections (each [redacted] mL) of [redacted] mg LEO 138559 or placebo to receive a total dose of 450 mg LEO 138559 or placebo ([redacted] mL). In addition to this Q2W dosing schedule, both treatment groups will receive an additional dose of their allocated treatment (LEO 138559 450 mg or placebo) at Visit 4 (Week 1). During the treatment period, final dosing will be administered at Week 14 and the clinical assessment will occur at Week 16. IMP administration will continue until Week 14, regardless of AD improvement.

IMP will be administered by a qualified, unblinded HCP as the preparation of the active drug is visually distinct from placebo (see Section 9.3.1 for blinding details). The IMP must be injected SC in the upper legs (thighs), stomach area (abdomen) or in the upper, outer arm but should not be given into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by AD. The anatomical location of the injection, and if it was on the right or left side, must be recorded in the source documents at each treatment visit and recorded in the eCRF.

At each treatment visit, the [redacted] injections of IMP must be administered within a maximum of 10 minutes. The [redacted] injections of IMP should be administered in the same injection site area (e.g. upper right arm) separated by at least 3 cm. The site of injection should be rotated such that the subject receives IMP at a different anatomical site at each treatment visit. If for some reason the injection site was not rotated, this should be documented, and a reason should be recorded in the eCRF.

If any issues with the IMP (e.g., damaged kit or vial/syringe) or a malfunction during administration should arise, the unblinded CRA should be contacted, and the issue should be documented.

Further details on IMP preparation and administration will be provided in an instruction for use and trial product handling manual. IMP administration must be carried out according to these instructions.

After IMP administration

For the first 3 IMP treatment visits (i.e., Visits 3, 4, and 5), subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 1 hour with vital signs taken immediately after IMP administration as well as after 30 minutes (± 5 minutes) and after 1 hour (± 5 minutes), or until stable, whichever is later. Vital signs will be documented in the eCRF.

As with any antibody, allergic reactions to dose administration are possible. The World Allergy Organisation has categorised anaphylaxis into 2 subgroups: allergic anaphylaxis (mediated by an immunologic mechanism) and nonallergic anaphylaxis (which has a nonimmunologic cause) (44). The clinical criteria for defining anaphylaxis for this trial are listed in Appendix 5 and (45). Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc., and medical equipment to treat acute anaphylactic reactions must be immediately available at trial sites, and trial personnel should be trained to recognise and respond to anaphylaxis according to local guidelines.

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

Conditions requiring IMP administration rescheduling

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

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

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

Overdose is specified in Section 13.6.2. LEO Pharma does not have any specific treatment recommendations in relation to overdose. The investigator will use clinical judgement to treat any overdose if necessary.

9.3 Treatment assignment

Subjects who comply with all the eligibility criteria (Sections 8.1, 8.2, and 8.3) will be randomised at baseline (Day 1) to receive treatment with either LEO 138559 450 mg Q2W or

placebo Q2W. Treatment assignment will be pre-planned according to a computer generated randomisation schedule in a 1:1 ratio (LEO 138559 : placebo) stratified by baseline disease severity; one stratum, 'stratum A', will be defined as having EASI <21 and the other stratum, 'stratum B', will be defined as having EASI ≥21.

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

9.3.1 Blinding

This is a double-blinded trial in which LEO 138559 and placebo are visually distinct from each other and not matched for viscosity. Neither the subject nor any of the investigators or LEO Pharma staff (except unblinded CRAs) who are involved in the clinical evaluation and monitoring of the subjects will be aware of the treatment received.

IMP will be prepared, handled, and administered by a qualified, unblinded HCP at the site who will not be involved in the management of trial subjects and who will not perform any of the assessments.

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

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

The trial site will maintain a written plan (site blinding plan) detailing which staff members are blinded/unblinded and the process of IMP administration used to maintain the blind.

9.3.2 Emergency unblinding of individual subject treatment

While the safety of a subject always comes first, it is still important to carefully consider if unblinding is necessary to ensure a subject's safety. An emergency unblinding request can be made by the investigators, HCPs who are not members of the trial staff, or authorised LEO 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 in the

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

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

LEO Pharma Global Safety may unblind subject(s) if it is deemed necessary, including for regulatory purposes in relation to reporting of SUSARs.

9.4 Background treatment (emollients)

All subjects must use an emollient twice daily (or more frequently, if needed) for at least 7 days before Day 1 (baseline) and throughout the treatment period (until Week 16). Subjects should use the same emollient throughout the trial.

The emollient should preferably not contain additives such as ceramide, hyaluronic acid, or urea. 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 moisturised in the absence of systemic and/or topical AD treatment(s) in the washout period (Week -1 to Week 0).
- Act as a complement to systemic treatment with the IMP (standard of care) and keep the subject's skin well moisturised in the treatment period (Week 0 to Week 16).

Reporting in eCRF
It will be recorded in the eCRF if background treatment (emollient) has been used daily; if not, a reason should be provided.

9.5 Rescue treatment

If medically necessary (i.e., due to worsening of AD or intolerable AD symptoms), rescue treatment for AD in the form of TCS/TCI may be prescribed to trial subjects and used from Week 4 at the discretion of the investigator. It is recommended that the investigator starts with

a TCI or least potent TCS for the face (e.g., hydrocortisone 2.5% cream/ointment) and moderately potent TCS for the body (e.g., triamcinolone acetonide 0.1% cream/ointment).

If rescue treatment with TCS/TCI is initiated after Week 4, the subject will continue treatment and the schedule of trial visits and assessments. However, treatment with IMP will be discontinued if a subject receives the following treatment:

- Rescue treatment with any TCS/TCI before Week 4.
- Super potent TCS (e.g., clobetasol propionate 0.05% cream) between Week -1 and Week 16.
- Systemic rescue treatment (besides systemic antihistamines and/or anti-infectives) at any point during the trial between Week -4 (or from 5 half-lives of Week 0, whichever is longer) and Week 16.

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

During the safety follow-up period (Weeks 16 to 32), topical therapy (including TCS and TCI) may be prescribed to control disease activity at the discretion of the investigator and will not be considered as rescue treatment. Any medication taken by the subjects during the follow-up period will be reported as concomitant medication using the eCRF.

Reporting in eCRF
It will be recorded in the eCRF if and what rescue treatment has been used.

9.6 Concomitant medication 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 treatment for AD.
- Indication.
- Start and stop date of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose per administration, unit, and frequency.

- Route of administration: oral, topical, SC, transdermal, intraocular, intramuscular, respiratory (inhalation), intralesional, intraperitoneal, nasal, vaginal, rectal, IV, or other (if other, a specification must be provided).
  For topical treatments, the dosage form (cream, lotion, ointment, other) and the potency will also be recorded.
  For topical, SC, transdermal, intramuscular, and intralesional treatments, the location of administration including laterality will also be recorded (e.g., left upper arm).

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

- Procedure name.
- Body location (upper limb, lower limb, trunk, head).
- Indication.
- Start and stop date (it will also be recorded if the procedure is ongoing).

It should be included whether the procedure is inside the area of injection or the area of an AD lesion.

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

The following concomitant medications are permitted during the trial:

- Paracetamol use (maximum 2 g/day).
- Concomitant therapies taken for the long-term treatment of pre-existing conditions can continue during the trial provided they are in accordance with the exclusion criteria (see Section 8.3).
- Systemic antihistamines and/or anti-infectives.
- Emollients allowed during the treatment period.

For AD patients with mild chronic asthma (42) or mild allergic rhinitis, use of inhaled corticosteroids up to and including 500 µg beclometasone (or equivalent) per day is acceptable.

9.7 Prohibited medication and procedures

Prohibited medications and/or procedures are listed in Panel 5. Details regarding prohibited medications and/or procedures prior to screening and during washout(s) are described 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).

Panel 5: Prohibited medication(s) and/or procedure(s)

Medication or procedure	Prohibited from	Prohibited to
TCS or TCI (other than those permitted as rescue treatment).	Washout (Week -1).	Week 16.
Topical PDE-4 inhibitors.	Washout (Week -1).	Week 16.
Other topical prescription medications or prescription emollients/moisturisers (other than the ones allowed during treatment period) used for the treatment of AD.	Washout (Week -1).	Week 16.
Use of UVA, UVB, PUVA, other phototherapy, or tanning beds.	Week -4 prior to randomisation.	Week 16.
Immunoglobulin or blood products.	Week -4 or 5 half-lives prior to randomisation, whichever is longer.	Safety follow-up (Week 32).
Systemic corticosteroids (excluding inhaled or intra-nasal steroids).	Week -4 prior to randomisation.	Safety follow-up (Week 32).
Systemic immunosuppressive/immuno-modulating medication (excluding systemic antihistamines).	Week -4 or 5 half-lives prior to randomisation, whichever is longer.	Safety follow-up (Week 32).
Biologics.	Week -16 or 5 half-lives prior to randomisation, whichever is longer.	Safety follow-up (Week 32).
Allergen immunotherapy.	Week -4 prior to randomisation.	Safety follow-up (Week 32).
Live (attenuated) vaccine.	Week -12 prior to randomisation.	Safety follow-up (Week 32).

Abbreviations: AD = atopic dermatitis; PDE-4 = phosphodiesterase-4; PUVA = psoralen ultraviolet A; TCI = topical calcineurin inhibitor(s); TCS = topical corticosteroid(s); UVA = ultraviolet A; UVB = ultraviolet B.

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

As described in Section 9.5, TCI and TCS used as rescue treatment for worsening of AD or intolerable AD symptoms are allowed from Week 4.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

IMP will be packed open label in individually numbered kits.

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

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 (46), local regulations, and trial requirements. Label text will be translated into local languages as required.

9.8.2 Storage of trial products

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.

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

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

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

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

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

Damaged IMP should be documented via IRT (refer to the IRT quick reference guide for further details). Damaged IMP should not be used.

9.8.3 Drug accountability

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

Dispensing of IMPs may be delegated, e.g., to a hospital pharmacy, as locally applicable.

Documentation of drug accountability must be kept of the IMPs administered to each individual subject randomised in the trial. This documentation must be available during monitoring visits and will be checked by the unblinded CRA to verify correct dispensing of the IMPs. Drug accountability information will be recorded in the IRT system. The IRT system will also maintain the inventory status of all IMPs at the trial site.

The IMP must be fully accounted for by the unblinded CRA with the help of the unblinded HCP. Accountability must be documented in the trial medication inventory log in the IRT.

For further information about handling of trial product at site, including IMP accountability, and reconciliation, please refer to the trial product handling manual.

9.8.4 Treatment compliance

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

Reporting in eCRF
The following data will be recorded in the eCRF:

Did the subject comply with the IMP dosing schedule (yes, no); If no, a reason will be given. It will also be recorded how much IMP the subject received (partial dose, no dose, and the total number of IMP applications missed since last visit).

- Primary reason for non-compliance – lack of time, adverse event, other (if other, a specification should be provided).
- Date and time of IMP administration (stated for each of the [redacted] injections).
- Site of IMP injection: For the site (upper leg [thigh], stomach area [abdomen] or in the upper, outer arm) the laterality should be specified (right or left).

9.8.5 Trial product destruction

Used IMP (i.e., empty vials) and unused IMP must be returned to the CMO for destruction. Used IMP and unused IMP that is no longer available for dispensation (e.g., expired or

damaged IMP) can be returned on an ongoing basis throughout the trial. Unused IMP (i.e., IMP that is still available for dispensation) can be returned for destruction after the last dosing visit of the last subject at the site.

Syringes used for administration of IMP can be destroyed at site according to local procedures in compliance with local regulations.

9.9 Provision for subject care following trial completion

In order to ensure appropriate treatment of the subjects after they have completed the trial, the subjects will be treated at the investigator's discretion or referred to other physician(s) according to standard practice.

9.10 Reporting product complaints

Any defects or issues with the IMP (e.g., inadequate labelling) must be reported to Global Safety at LEO Pharma on the trial-specific (paper) complaint form within 3 days of first knowledge.

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

Complaint forms should contain a detailed description of the defect or 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 Sections 13.3 and 13.4.

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

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:
Fax number: +45 6910 2468
E-mail address: drug.safety@leo-pharma.com

10 Discontinuation and withdrawal

10.1 General principles

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

A subject who withdraws from the trial is a subject who stops treatment with the IMP and all further protocol defined trial activities. A subject who permanently discontinues IMP is a subject who, although they stop treatment with the IMP, agree to their follow-up as described in Section 10.3. Early termination assessments to be conducted for both events are described in Section 10.3.

Subjects who withdraw from the trial and subjects who permanently discontinue IMP 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 discontinuation of IMP

10.2.1 Reasons for permanent discontinuation of IMP

Subjects will permanently discontinue IMP in the event of:

- Withdrawal of consent.
- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.
- Initiation of systemic rescue treatment of AD (besides systemic antihistamines and/or anti-infectives) at any point during the trial between Week 0 and 16, rescue treatment before Week 4, and/or super potent TCS between Week -1 and Week 16.
- Initiation of prohibited medication which cannot be safely replaced by other non-prohibited medications.
- Evidence of pregnancy, or if the subject is noncompliant with the contraception requirements (see Section 8).
- Other reasons, at the discretion of the investigator. If other, a specification should be provided.

Reporting in eCRF
The date and time of last dose for IMP will be recorded in the eCRF. The primary reason for permanent discontinuation of IMP must be recorded in the medical records and on the end-of-treatment form in the eCRF where the following options are available:

- Pregnancy.
- Adverse event (if adverse event, a specification must be provided).
- Lack of efficacy.
- Withdrawal by subject.
- Lost to follow-up.
- Other (if other, a specification should 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.

10.2.2 Reasons for temporary discontinuation of IMP

IMP dosing may be temporarily suspended in the event of:

- COVID-19 related disruption.

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

10.3 Early termination assessments

Permanent discontinuation of IMP
Subjects who permanently discontinue IMP for any reason will be asked to attend an early termination visit as soon as possible after last administration of IMP and return to the trial site for additional visits as indicated below. See the schedule of trial procedures (Section 4) for data to be collected at these visits. Subjects who discontinue IMP but remain in the trial will continue completing the eDiary until the safety follow-up visit (Visit 16). The investigator will review any AEs which will be followed up according to Section 13.7, if the subject agrees.

Subjects who permanently discontinue IMP will be asked to attend:

- An early termination visit as soon as possible after last dose of IMP.
- The primary endpoint visit (16 weeks after randomisation).
- A safety follow-up visit (16 weeks after last administration of IMP).

Details on data to be recorded in the eCRF for subjects who permanently discontinue IMP can be found in Section 11.7.

Withdrawal from trial
Subjects who withdraw/are withdrawn from the trial prior to first dose of IMP (randomisation) will be considered screening failures.

Subjects who withdraw from the trial for any reason should attend an early termination visit as soon as possible after last administration of IMP. Assessments/procedures to be conducted at this visit are listed in the schedule of trial procedures (Section 4). If the subject agrees, the investigator will review any AEs which will be followed up according to Section 13.7.

Details on data to be recorded in the eCRF for subjects who withdraw from the trial can be found in Section 11.7.

10.4 Lost to follow-up

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

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

- The trial site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to 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) and will be conducted in the order presented in Panel 6. PROs to be completed at the trial site and investigator assessments of efficacy should be conducted at the same visit.

Panel 6: Sequence of assessments

[a] At the screening visit (at the earliest Week -4), the subject's eligibility to participate in the trial must be confirmed before any PROs are completed. PROs will be completed either in the eDiary or on an electronic device at the trial site.
[b] Laboratory assessments include PK and PD samples. PD samples include serum biomarkers, skin swabs, and tape strips.
[c] For the first 3 IMP treatment visits (i.e., Visits 3, 4, and 5) subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 1 hour with vital signs taken immediately after IMP administration as well as after 30 minutes (± 5 minutes) and after 1 hour (± 5 minutes), or until stable, whichever is later.

Subjects participating in the trial will be under careful supervision of a qualified principal investigator who must be a dermatologist or an allergist. Investigators must be physicians and have experience in treating AD as well as documented experience with and/or training in the assessments used in this trial. All dermatologic assessments must be performed by a

dermatologist or an adequately qualified medical doctor (defined as someone with at least 1 year post graduate experience).

AEs must be assessed by a physician (Section 13.2).

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

The investigators performing the assessments must not be involved in the administration of IMP (Section 9.3.1).

11.2 Assessments performed only at screening/baseline

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.
- Race: American Indian or Alaska native, Asian, Black or African American, native Hawaiian or other Pacific islander, White, other (if other, a specification should be provided).
- Ethnic origin (self-reported by the subject, Hispanic or Latino, not Hispanic or Latino), if allowed by the local legislation.

At baseline, only age will be recorded (Section 4).

11.2.2 Body assessment (height)

Height will be recorded according to the schedule of trial procedure (Section 4).

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

11.2.3 Medical history

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

Relevant past and concurrent medical history must be recorded including all past and current skin disease history:

- Atopy history:
  - Age at first onset of AD.
  - Previous AD treatments (e.g., dupilumab, cyclosporine, etc).
  - Asthma.
  - Food allergy.
  - Hay fever.
- Other medical and surgical history including concurrent diagnoses within the previous 12 months. 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 Other assessments

The following tests will be conducted according to the schedule of trial procedures (Section 4):

- Hepatitis B virus testing (for more detail, see Panel 10).
- Hepatitis C virus antibody.
- HIV antibodies.
- Tuberculosis (*Mycobacterium tuberculosis* IFN-γ release assay [or a PPD test if a requirement from the local health authorities]).
- SARS-CoV-2 (PCR).

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). At an unscheduled visit, it will be at the discretion of the investigator if EASI should be assessed.

EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (47). 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. To reduce inter-assessor variability, the same investigator should, whenever possible, conduct all EASI assessments for a given subject during the entire trial.

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 7. Briefly, the investigator will assess the severity of 4 AD disease characteristics (erythema, induration/papulation, excoriation, and lichenification) on the 4 body regions (head/neck, trunk, upper extremities, and lower extremities). Severity will be assessed using the severity score scale presented in Panel 8. For each body region, a severity sum score will be calculated and multiplied by an area score (Panel 8) and a weighting factor. The EASI score equals the sum of scores obtained for each body region (Panel 7).

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. Refer to Appendix 3D for principles for data entry in the eCRF.

Panel 7: Calculation of the Eczema Area and Severity Index

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

Abbreviations: AS = area score; EASI = Eczema Area and Severity Index; SS = severity score.
Modified from (48).

Panel 8: Eczema Area and Severity Index severity score scale and area score scale

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

[a] Half-scores (0.5, 1.5, 2.5) are allowed.

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

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). At an unscheduled visit, it will be at the discretion of the investigator if the vIGA-AD should be assessed.

The vIGA-AD is an instrument used in clinical trials to assess the subject's global disease severity and is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Panel 9) (49). 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 assessment score will be recorded in the eCRF. Refer to Appendix 3D for principles for data entry in the eCRF.

Panel 9: Validated Investigator Global Assessment Scale for Atopic Dermatitis

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, and 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 or crusting may be present.

11.3.3 Body surface area involvement

The total BSA score will be assessed according to the schedule of procedures (Section 4).

The investigator will assess the total AD involvement for the whole body, i.e., head/neck, upper extremities, trunk, genitalia, and lower extremities, as a percentage of the total BSA. As a guidance for this estimate, the surface of a full, flat palm (including the 5 fingers) of an adult subject corresponds to approximately 1% of the total BSA.

11.3.4 Patient-reported outcomes

11.3.4.1 Overview

During the trial each subject should make individual assessments relating to their perception of their disease and quality of life. These should be performed independently of the investigator and prior to the investigator performing his/her efficacy assessments. At the screening visit (at the earliest Week -4), the subject's eligibility to participate in the trial needs to be established before the PROs can be completed.

The subject will be asked to complete the following PROs according to the schedule of trial procedures (Section 4).

- Worst Daily Pruritus NRS.
- POEM.
- DLQI.

Worst Daily Pruritus NRS will be completed daily in an eDiary. At Week -1 subjects will receive an eDiary device and eDiary training in using the device. At each visit between Week -1 and Week 32, the investigator or site staff will review the eDiary on the eDiary vendor portal and check compliance with eDiary completion.

In case of significant non-compliance, the investigator should remind the subject of the importance of adhering to the eDiary completion schedule. Subjects will be asked to return the eDiary at Week 32 or at their last visit in the trial.

POEM and DLQI will be completed in an electronic device by the subjects at the trial sites at the visits specified in the schedule of trial procedures (Section 4). At an unscheduled visit, it will be at the discretion of the investigator if POEM and/or DLQI should be assessed.

11.3.4.2 Worst Daily Pruritus NRS

Subjects will assess their worst itch severity over the past 24 hours using an 11-point NRS ('Worst Daily Pruritus NRS') with 0 indicating 'no itch' and 10 indicating 'worst itch imaginable'. Subjects will complete the Worst Daily Pruritus NRS as part of an eDiary each day from Week -1 until Week 32.

11.3.4.3 Patient-Oriented Eczema Measure (POEM)

The POEM is a validated questionnaire used to assess disease symptoms in AD patients in both clinical practice and clinical trials (50). The tool consists of 7 items each addressing a

specific symptom (itching, sleep, bleeding, weeping, cracking, flaking, and dryness). Subjects will score how often they have experienced each symptom over the previous week on a 5-point categorical response scale (0 = 'no days'; 1 = '1 to 2 days'; 2 = '3 to 4 days'; 3 = '5 to 6 days'; 4 = 'every day'). The total score is the sum of the 7 items (range 0 to 28) and reflects disease-related morbidity; a high score is indicative of a worse disease severity.

11.3.4.4 Dermatology Life Quality Index (DLQI)

The DLQI is a validated questionnaire with content specific to those with dermatology conditions (51). It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their quality of life over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment . Each item is scored on a 4-point Likert scale (0 = 'not at all /not relevant'; 1 = 'a little'; 2 = 'a lot'; 3 = 'very much'). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor quality of life.

11.4 Safety assessments

11.4.1 Vital signs

Vital signs (blood pressure, pulse, and body temperature) will be assessed according to the schedule of trial procedures (Section 4). At an unscheduled visit, it will be at the discretion of the investigator if vital signs should be assessed.

For the first 3 IMP treatment visits (i.e., Visits 3, 4, and 5) subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 1 hour with vital signs taken immediately after IMP administration as well as after 30 minutes (± 5 minutes) and after 1 hour (± 5 minutes), or until stable, whichever is later.

Vital signs (blood pressure, pulse, and body temperature) will be assessed 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 measurement (abnormal), 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 a clinically significant abnormal vital sign at screening and/or baseline, it will be at the discretion of the investigator if the subject should be included in the trial in accordance with exclusion criterion no. 27. During the trial, if a subject presents with a clinically significant abnormal 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. Clinically significant abnormal vital signs at screening and baseline will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom, or illness occurring after randomisation will be reported as an AE in accordance with Section 13.3.

Refer to Appendix 3D for principles for data entry in the eCRF.

11.4.2 Physical examination

A physical examination of the subject including general appearance, regional lymph nodes, and dermatologic examination of the skin will be performed according to the schedule of trial procedures (Section 4). At an unscheduled visit, it will be at the discretion of the investigator if a physical examination should be performed.

In case of a clinically significant abnormal finding during physical examination at screening and/or baseline, it will be at the discretion of the investigator if the subject should be included in the trial in accordance with exclusion criterion no. 27. During the trial, if a subject presents with a clinically significant abnormal 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.

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

Refer to Appendix 3D for principles for data entry in the eCRF.

11.4.3 Weight

Weight will be recorded according to the schedule of trial procedures (Section 4). The subject's weight (in indoor clothing and without shoes) will be measured. At an unscheduled visit, it will be at the discretion of the investigator if weight should be measured.

11.4.4 ECG

ECGs must be measured according to the schedule of trial procedures in (Section 4). At an unscheduled visit, it will be at the discretion of the investigator if an ECG should be measured.

At each visit, the individual measurements as well as the average of 3 consecutive 12-lead resting digital ECG measurements will be recorded after the subject has been in supine position for at least 5 minutes.

A pre-evaluation of the ECGs will be performed by the investigator to evaluate immediate subject safety. At a minimum, the date of ECG pre-evaluation will be recorded in the source documents. In case of a suspected abnormal ECG, the investigator must take appropriate action, at their discretion.

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

The investigator must evaluate all abnormal ECG results ('clinically significant' or 'not clinically significant') and sign and date when the evaluation is performed. The investigator has the final decision on the clinical significance of ECG abnormalities.

If a result is abnormal at the screening or baseline visit and considered by the investigator to be clinically significant, it will be up to the investigator's discretion to decide if the subject should be enrolled into the trial (respecting exclusion criteria no. 18 and 27). If a subject with an abnormal and clinically significant ECG result is enrolled, the investigator should provide a justification in the medical record.

During the trial if a subject presents with a clinically significant abnormal ECG or a clinically significant abnormal change in ECG from baseline, the ECG should be repeated. If the ECG or change in ECG is confirmed clinically significantly abnormal, the subject must permanently discontinue IMP, and be withdrawn from the trial. In such case, the subject

should be monitored until the subject's ECG returns to a state similar to that of screening/baseline at the discretion of the investigator.

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. The date of ECG measurement must be recorded. In case of a suspected abnormal ECG, the action taken with the subject, if any, must be recorded. The investigator's assessment of ECG result ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant') must also be recorded in the eCRF.

Clinically significant abnormal ECG findings at screening and baseline before first dose of IMP will be documented as medical history in the eCRF. At subsequent visits, any new clinically significant abnormal ECG finding, symptoms, or illnesses, as well as any clinically significant deterioration of a pre-existing condition after randomisation will be reported as an AE as described in Section 13.3.

Refer to Appendix 3D for principles for data entry in the eCRF.

11.4.5 Laboratory testing

11.4.5.1 Overview

Blood and urine samples will be collected according to the schedule of trial procedures (Section 4) and the evaluations listed in Panel 10 will be conducted by the central laboratory. At an unscheduled visit, it will be at the discretion of the investigator if samples should be collected.

Panel 10: Clinical laboratory tests

Clinical chemistry	Haematology
Sodium Potassium Creatinine Urea nitrogen Calcium Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma glutamyl transferase Bilirubin[1] (Direct bilirubin)[1] (Indirect bilirubin)[1] Cholesterol LDL cholesterol HDL cholesterol Triglycerides Glucose (non-fasting) Albumin Protein Tryptase[2] Lactate dehydrogenase C-reactive protein	Haematocrit Haemoglobin Leukocytes Neutrophils Neutrophils/leukocytes[5] Lymphocytes Lymphocytes/leukocytes[5] Monocytes Monocytes/leukocytes[5] Eosinophils Eosinophils/leukocytes[5] Basophils Basophils/leukocytes[5] Thrombocytes
Serology	**Tuberculosis test[6]**
Hepatitis B virus surface antigen[3] Hepatitis B virus surface antibody[3] Hepatitis B virus core antibody[3] Hepatitis C virus antibody[3] HIV-1 antibody[3] HIV-2 antibody[3] Immunoglobulin E	*Mycobacterium tuberculosis* IFN-γ release assay
	COVID-19 test
	SARS-CoV-2 (PCR)[3]
Urinalysis[4]	**Serum pregnancy test[7]**
Protein Glucose Ketones Occult blood Leukocytes Nitrite	β-human chorionic gonadotropin

1) If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
2) In case of reactions to SC IMP administration, tryptase can be tested at the discretion of the investigator.
3) Conducted at screening only.
4) The analytes listed will only be measured if the urine dipstick is abnormal.
5) The symbol '/'included in the table represents 'a ratio'.
6) Conducted at screening only.
7) Only women of childbearing potential.

Abbreviations: HDL = high density lipoprotein; HIV = human immunodeficiency virus; IMP = investigational medicine product; LDL = low density lipoprotein; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = subcutaneous.

11.4.5.2 Investigator evaluation of laboratory samples

Laboratory samples sent to the central laboratory

Clinical chemistry, haematology, urinalysis (if applicable), serology, and serum pregnancy tests will be analysed by a central laboratory which will provide results to the trial sites. 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 randomised in the trial in accordance with exclusion criterion no. 22. 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 the interpretation of the initial test results for hepatitis B, hepatitis C, or HIV, these will be conducted by the central laboratory, as applicable. Subjects with a positive serology, tuberculosis, or SARS-CoV-2 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 analysed by a central laboratory which will provide results to the trial sites. A woman with a positive serum pregnancy test at screening must not be included in the trial (inclusion criterion no. 10 and exclusion criterion no. 23).

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 performed at the trial site

Urine samples will be tested at the trial site with a dipstick according to the schedule of trial procedures (Section 4). At an unscheduled visit, it will be at the discretion of the investigator if urine samples should be collected.

If a dipstick shows any abnormal reading, a urine sample must always be collected and sent to the central laboratory for further analysis, regardless of causality or investigator's assessment of significance.

Urine pregnancy tests for women of childbearing potential will be conducted at the trial sites. A woman with a positive urine pregnancy test at Week 0 (baseline) must not be randomised in the trial (inclusion criterion no. 10 and exclusion criterion no. 23). The test will be repeated every 4 weeks until Week 16 and at Week 32 as shown in the schedule of trial procedures in Section 4. A woman with a positive urine pregnancy test during the trial 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.

Reporting in eCRF
It will be recorded in the eCRF if a blood sample was taken. 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.

Clinically significant abnormal laboratory results at screening and baseline will be documented as medical history in the eCRF. At subsequent visits, any new clinically significant abnormal laboratory results, symptoms, or illnesses, as well as any clinically significant deterioration of a pre-existing condition after randomisation will be reported as an AE as described in Section 13.3.
Refer to Appendix 3D for principles for data entry in the eCRF.

11.4.6 Anti-drug antibodies measurements

Blood samples will be collected to determine ADA levels at pre-determined time points according to the schedule of trial procedures (Section 4). At an unscheduled visit, it will be at the discretion of the investigator if a blood sample to determine ADA levels should be collected.

Serum samples for determination of presence or absence of ADA will be analysed by a laboratory using a validated bioanalytical method. A tiered testing scheme will be employed,

with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titre determination. Details of the analytical method used will be described in a bioanalytical report.

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

ADA A samples will be discarded upon finalisation of the CTR, whereas ADA B samples will be retained until approval in first major market (EU, US, and JP) or until 10 years after final CTR – whichever comes last.

Reporting in eCRF
It will be recorded in the eCRF if an ADA blood sample was taken. If not, a reason should be provided. Refer to Appendix 3D for principles for data entry in the eCRF.

11.5 Pharmacokinetic assessments

11.5.1 Blood sampling for analysis of PK

Blood samples for PK assessments will be collected at the time points specified in the schedule of trial procedures (Section 4). At an unscheduled visit, it will be at the discretion of the investigator if a blood sample to determine PK should be collected.

Serum samples for determination of LEO 138559 concentrations will be analysed by a laboratory using a validated bioanalytical method.

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

Reporting in eCRF
It will be recorded in the eCRF if the PK sample was taken; if not, a reason will be provided. Refer to Appendix 3D for principles for data entry in the eCRF.

11.6 Pharmacodynamics assessments

11.6.1 Overview

Biomarker expression in blood and skin (skin swabs and tape strips) will be measured to evaluate treatment effect of LEO 138559 on disease biomarkers and biomarkers related to the mechanism of action of LEO 138559 as presented in Sections 11.6.2, 11.6.3, and 11.6.4.

The biomarker assessments are considered exploratory. A summary of the results will be included in the CTR if the results are available in time for this. The full pharmacodynamics/biomarker results will be reported in an addendum to the CTR.

11.6.2 Blood biomarkers

Serum samples for biomarker analyses will be collected according to the schedule of trial procedures (Section 4). At an unscheduled visit, it will be at the discretion of the investigator if a blood sample should be collected to determine blood biomarkers.

The serum biomarkers to be analysed include, but are not limited to CCI CCI .

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

Serum biomarker data will be described in a separate report appended to the CTR.

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

Refer to Appendix 3D for principles for data entry in the eCRF.

11.6.3 Skin swabs

Skin swabs will be taken according to the schedule of trial procedures (Section 4). At an unscheduled visit, it will be at the discretion of the investigator if skin swabs should be taken.

Skin swabs from both lesional and non-lesional skin will be performed to measure the abundance of *S. aureus* colonisation as well as for broad microbiome profiling based on 16 S rRNA sequencing at baseline and Week 16. Subjects will be asked not to shower, bathe, or wash in general within 12 hours prior to the baseline and Week 16 visits.

S. aureus colonisation will be analysed by qPCR. In addition, the skin microbiome may be characterised using next-generation sequencing.

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

Results from skin swabs will be described in a separate report appended to the CTR.

Reporting in eCRF

It will be recorded in the eCRF if skin swabs were taken and from which body location (volar arm, elbow pit, trunk, lower limbs, other) it was taken. If skin swabs were not taken, a reason should be provided.

Refer to Appendix 3D for principles for data entry in the eCRF.

11.6.4 Tape strips

Tape stripping will be performed according to the schedule of trial procedures (Section 4). At an unscheduled visit, it will be at the discretion of the investigator if tape stripping should be performed.

Non-invasive tape stripping will be done to investigate gene expression in the skin. At baseline, the assessment will be done in 2 areas: in a representative lesional area and in a non-lesional area which is anatomically similar to the lesional area. If an anatomically similar non-lesional area cannot be found, the volar forearm may be used instead. At the end-of-treatment visit (or early IMP termination visit, if applicable) both the original lesional and a non-lesional area will be sampled. Note that the lesion sample at the end-of-treatment (or early IMP termination visit, if applicable) should be taken from the original lesional area, even if this lesion clears during the trial.

Subjects will be instructed not to apply any emollients for at least 2 hours prior to visits that include tape stripping.

Collection, handling, and shipment instructions for tape strips samples are provided in a laboratory manual.

Reporting in eCRF

It will be recorded in the eCRF if the tape strips were collected and from which body locations (volar arm, lower limbs, trunk, other).

Refer to Appendix 3D for principles for data entry in the eCRF.

11.7 End-of-trial

End-of-treatment form

An end-of-treatment form will be completed in the eCRF for all subjects when they have had their last administration of IMP. This form will also be completed for subjects who permanently discontinue IMP and subjects who withdraw from trial (see Section 10.3 for early termination assessments).

The date and time of last administration of IMP will be recorded on the end-of-treatment form. It will also be recorded if the subject completed the treatment. If not, the primary reason for permanent discontinuation of IMP must be recorded (see Section 10.2.1).

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

- Did the subject complete 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 withdrawal from trial (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 primary endpoint visit (Week 16). If not, the primary reason for not attending the visit (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 32). If not, the primary reason for not attending the visit (see reasons above) should be provided.

The end-of-trial form will be completed when the subject has had their last visit (that is, the follow-up visit at Week 32, or early termination visit, or primary endpoint visit).

11.8 Estimate of total blood volume collected

Blood samples will be drawn for haematology, biochemistry, serology, PK, PD, ADA, and safety assessments. The total volume of blood to be drawn is approximately 200 mL. If additional blood samples are required, the amount of blood drawn may be more than this stated value; however, the total volume of blood drawn will be less than that taken during a blood donation (approximately 500 mL).

11.9 Storage of biological samples

Primary samples (set A samples) for PK will be discarded by the bioanalytical lab upon finalisation of the CTR whereas backup samples (set B samples) stored at the central laboratory will be retained no longer than 12 months after completion of the CTR.

Primary samples (set A samples) for ADA evaluation will be discarded by the bioanalytical lab upon finalisation of the CTR whereas backup samples (set B samples) stored at the central laboratory will be retained until approval in first major market (US, EU, and JP) or until 10 years after final CTR – whichever comes last. Any B samples that have been sent to the bioanalytical lab will also be discarded upon finalisation of the CTR. The B samples stored at the central laboratory will be transferred to a central archive facility for long-term storage upon finalisation of the CTR.

Biobank

This protocol includes the collection and analysis of different biological samples. If consent is given by the subject, LEO Pharma will store serum, skin swab, and tape strip samples collected in a biobank established by LEO Pharma and hosted by Brooks Life Sciences GmbH (Germany). The biobanked biological samples will be used for future research performed by LEO Pharma. Donation of the samples for future research is voluntary and subjects must give their written consent to confirm donation and storage and the terms associated herewith. The samples will be transferred from the relevant laboratory to the biobank. The samples will be labelled with the trial ID, subject ID, and the sample date to protect the privacy of the subjects and to allow continued blinding for future analyses. The samples in this trial will be stored in the biobank for a maximum of 15 years after CTR finalisation, 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 is designed to evaluate the efficacy and safety of SC administered LEO 138559 450 mg Q2W compared with placebo Q2W in adults with moderate to severe AD. The trial design is considered appropriate to evaluate the trial objectives (Section 6).

Population
The most important inclusion criterion for participation in the trial is an established diagnosis of AD (as defined by the AAD Consensus Criteria (1) with a history of AD of at least 1 year prior to screening), to ensure correct diagnosis and rule out differential diagnosis (Section 8.2). The AAD Consensus Criteria are utilised in clinical trials and in clinical practice for the diagnosis of AD. The AAD Consensus Criteria are based on the long standing Hanifin and Rajka criteria (52) but are updated to emphasise both childhood and adult aspects of AD.

Another prerequisite for participation in the trial is a recent (within 6 months prior to the screening visit) documented history of inadequate response to topical AD treatments or being a subject for whom topical treatment is medically inadvisable, to ensure that the subject is candidate for the treatment.

The other eligibility criteria have been chosen to ensure inclusion of the targeted patient population and safety of the subjects and to minimise factors which could interfere with the efficacy and safety assessments (Sections 8.2 and 8.3).

Treatment and treatment groups
Based on PK, PD, and safety results of the FiM trial with LEO 138559 (LP0145-1315), the dose regimen LEO 138559 450 mg Q2W was selected for investigation in this trial.

In addition to the Q2W dosing schedule, an additional dose of IMP will be given to the subjects at Week 1 to reach steady state exposure early in the treatment period. According to a PK model developed based on preliminary data from the FiM trial, the additional dose given at Week 1 should allow 75% of steady state exposure to be reached already after 3 weeks of treatment.

The placebo control group will serve as reference to evaluate the efficacy and safety of LEO 138559. The use of a placebo control group allows for an evaluation of similarity to the

treatment effect observed in other AD systemic treatment trials, thereby adding to the knowledge needed for positioning LEO 138559 in the AD treatment pathway.

Trial periods

The screening period should last long enough to allow complete washout of any systemic AD treatment by Week 0 (baseline) but should not exceed 4 weeks in total so that the general medical condition of the subject, as established by the examinations and laboratory measurements conducted at the screening visit, has not significantly changed by Week 0 (Section 7.1).

The 1-week washout period is considered an appropriate length to ensure washout of any topical AD treatment (TCS/TCI) and establish a baseline for AD symptoms. In this period, the subject should apply a background treatment (emollient) on lesional and non-lesional skin at least twice daily for at least 7 consecutive days prior to baseline to keep their skin well moisturised in the absence of systemic and/or topical AD treatment(s) (Section 7.1).

AD is a chronic condition with a waxing and waning course. Subjects with moderate to severe AD often experience multiple flares during the course of a year and therefore a 16-week treatment period ensures sufficient time to evaluate the impact of LEO 138559 on disease severity. Further, given the expected half-life, dosage, and dosing frequency of LEO 138559, a 16-week treatment period ensures that LEO 138559 will reach its maximum effect. During the treatment period, the subject will be asked to continue applying an emollient twice daily (or more frequently, if needed) as a complement to the systemic treatment (standard of care) and to keep their skin well moisturised (Section 7.1).

After last dose of IMP, the 16-week safety follow-up period is considered an appropriate length before the last safety assessments are conducted (Section 7.1).

Mitigation of bias

The combination of randomisation and blinding (Section 9.3.1) minimises the likelihood of allocation bias. The risk of allocation bias is further reduced through the use of central randomisation. The use of randomisation also ensures that baseline factors will not be confounded with treatment. Randomisation within the strata defined by baseline disease severity (‘stratum A’ [EASI <21] or ‘stratum B’ [EASI ≥21]) will limit any potential imbalance in the allocation of subjects across baseline disease severity.

Endpoints and estimands

The endpoints have been selected to evaluate the efficacy of LEO 138559 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 138559 (53).

The primary estimand addressing the primary endpoint follows a hypothetical strategy which attempts to quantify the effect of treatment, in the hypothetical situation, where one or more intercurrent events (initiation of rescue treatment or permanent discontinuation of IMP) do not occur.

12.2 Appropriateness of assessments

Efficacy assessments
EASI and vIGA-AD are validated measures used in clinical practice and clinical trials by investigators to assess the severity and/or extent of AD (see Sections 11.3.1 and 11.3.2) (47-49).

PROs
A range of validated PROs will be used to assess subject perception of AD independently of the investigator or trial staff. The PROs have been selected to assess the key symptoms of AD (including itch) and HRQoL (11.3.4).

Safety assessments
Standard clinical methods of subject evaluations, such as AE monitoring (Section 13), vital signs, physical examinations, ECG, laboratory testing including pregnancy testing, and ADA will be used to assess subject safety (Section 11.4). Given some large proteins may cause indirect adverse cardiac effects upon long term exposure, data on ECG will be collected and evaluated (11.4.4). Data on ADA will be collected in order to evaluate the potential immunogenicity of LEO 138559 (11.4.6).

One AESI of lower respiratory tract infection has been identified for this trial as IL-22 has been shown to mediate mucosal host defence of the lung and induce expression of epithelial antimicrobial peptides (13.6.1). Therefore, when blocking IL-22R, there is a potential for increased risk of infection. However, no SAEs were reported in the FiM trial (LP0145-1315) nor in subjects with AD treated with a mAb targeting IL-22 (fezakinumab) (36). Further, IL-22R is expressed on epithelial cells and not on immune cells, so immune cell responses to

infections are preserved. For further information please refer to the current investigator's brochure (35).

Pharmacokinetic assessments
Serum concentration of LEO 138559 will be measured to further characterise the PK of LEO 138559 in subjects with moderate to severe AD (Section 11.5). The serum concentrations will be summarised and reported in the CTR as well as subjected to population PK analysis and reported separately, and may be used in an exploratory exposure-response analysis to support dose selection in future clinical trials.

Pharmacodynamics assessments
Biomarkers will be evaluated in blood and skin of subjects to assess 1) target engagement in the skin, 2) the molecular response of LEO 138559 on inflammatory processes in AD in general and more specifically on the IL-22 pathway, and 3) to identify sub-populations of AD patients with increased response to treatment.

Serum samples from all subjects will be collected for assessment of PD markers in the blood. Serum samples will be analysed for IL-22 pathway protein biomarkers, protein biomarkers of relevance for AD, and for potential new disease or treatment-related protein biomarkers.

Skin swabs will be taken from both lesional and non-lesional skin to measure the abundance of *S. aureus* colonisation as well as for broad microbiome profiling based on 16 S rRNA sequencing.

Transcriptome profiling of tape strips will be used to further elucidate the pathophysiological mechanisms of AD and to expand our understanding of the compound MoA. Biomarkers in tape strips will be assessed by RNA expression analysis.

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 ICF until completion of the clinical trial (all trial periods including safety follow-up visit at Week 32, see Section 7.3).

AEs must be assessed by a physician. In the US only, certain AE assessments can be delegated to investigators with other qualifications. However, the diagnosis, seriousness, and causality of the AEs must be assessed by a physician.

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

Principles for data entry in the eCRF are described in Sections 11.4.1 to 11.4.5.

13.3 Reporting of adverse events

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

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

The *duration* of the AE must be reported by the start date and stop date of the event (if the event is ongoing it will also be recorded). 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 discontinued, not applicable, unknown).

Other action taken: any other action taken as a result of the AE must be recorded (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. This report should contain an assessment of available information on seriousness, severity, causal relationship to the IMP or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event.

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 report.

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

Global Safety at LEO Pharma

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

Fax number: +45 6910 2468

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

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

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

SAEs occurring after the completion of the clinical trial 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 or not an SAE is expected. The relevant reference safety information document for this clinical trial is the investigator's brochure Section 7.4, edition 4.0 and subsequent updates (35).

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** (54), and which are unexpected (suspected, unexpected serious adverse reactions [SUSARs]), are subject to expedited reporting to regulatory authorities, IEC(s)/IRB(s) according to the current applicable legislation in the concerned countries. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

For the US, the following reporting requirements apply: all SAEs which are assessed as causally related to the IMP(s) **by LEO Pharma** (55, 56) and which are unexpected (serious and unexpected suspected adverse reactions [IND safety report]) are subject to expedited reporting to regulatory authorities and IRB(s). Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

13.5 Other events that require expedited reporting

13.5.1 Pregnancy

Any pregnancy occurring 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 final outcome must be reported on the (paper) pregnancy form (part II) within 24 hours of first knowledge.

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

Pregnant subjects must immediately discontinue IMP permanently and be withdrawn from the trial (Sections 10.2.1 and 10.3).

13.6 Reporting of other events

13.6.1 Adverse events of special interest

The event listed in Panel 11 is considered an AESI in this trial and will require additional details to be recorded. LEO Pharma may request that the investigator to forward additional test results, as appropriate. An AESI may be serious or non-serious. Serious AESIs require expedited reporting as described in Section 13.4.

Panel 11: Adverse events of special interest

AESI	Additional data to be recorded	Data collection method
Lower respiratory tract infections	• Infectious cause. • COVID-19 test performed in relation to event. • Known risk factors. • Smoking.	eCRF

Abbreviations: AESI = adverse events of special interest; eCRF = electronic case report form; COVID-19 = coronavirus disease 2019.

13.6.2 Overdose

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

The term ‘overdose’ including a specification of why it occurred (accidental or intentional) must be recorded on the AE form of the eCRF. In addition, AEs originating from overdose

must be recorded as separate events. If the AE originating from the overdose qualifies as an SAE, expedited reporting is required (Section 13.4).

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

13.6.3 Medication error

Medication error refers to any unintentional error in the dispensing or administration of an IMP. Medication errors include accidental overdose or underdose, inappropriate schedule of product administration, incorrect route of product administration, wrong product administered, and expired product administered.

Accidental overdose or underdose where a clinical consequence occurred or could have occurred should be recorded based on investigator judgement.

Inappropriate schedule of product administration where a clinical consequence occurred or could have occurred should be recorded based on investigator judgement. Treatment non-compliance (incl. missed doses) where no clinical consequence occurred or could have occurred should not be recorded as medication errors. See Section 9.8.4 for recording of treatment compliance.

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

13.6.4 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 protocol.

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 an 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 consequences of misuse/abuse must be recorded as separate AEs on the AE form. If the AE

originating from the misuse or abuse qualifies as an SAE, expedited reporting is required (Section 13.4).

13.6.5 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 Sections 13.3 and 13.4.

13.7 Follow-up for final outcome of adverse events

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

13.8 Handling of an urgent safety measure

An urgent safety measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined as *"…the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard.*" (57).

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

At baseline, a total of 52 subjects will be randomised 1:1:

- 26 subjects to LEO 138559 450 mg Q2W.
- 26 subjects to placebo Q2W.

The sample size is determined using t-test for pairwise consideration of 2 treatment groups based on the following assumptions:

Treatment	Expected reduction in EASI (SD)*	Attrition rate
LEO 138559	22.9 (13)	30%
Placebo	7.3 (18)	30%

*Expected reduction in EASI for LEO 138559 is based on results from an upadacitinib phase 2b trial (28), and for placebo, the expected reduction is based on a dupilumab phase 2b trial (58).

With a significance level of 5%, 18 subjects per treatment group will provide a nominal power of at least 80% to detect a difference between the 2 treatment groups. Assuming a maximum attrition rate of 30%, 26 subjects in each treatment group should be randomised into the trial.

Assuming a screening failure rate of 35%, the planned number of subjects to screen is set to 80.

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

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

A safety analysis set (SAF) will be defined as all subjects who will be exposed to IMP.

A PK analysis set will be defined as all subjects who will be exposed to LEO 138559 and provide samples for measuring serum concentrations of LEO 138559.

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 randomisation 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 safety analysis set. PK analysis will be based on the PK analysis set.

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

An observed cases approach will be used for tabulations of data by visit (that is, involving only those subjects who attended each specific visit). For categorical endpoints, the number of subjects not attending each specific visit will also be provided.

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

In general, for endpoints evaluated as change from baseline and/or where a baseline adjustment is applied, baseline is defined as assessments conducted at the randomisation visit (Visit 3), if not otherwise stated. If the information is not available at the randomisation visit but at the (re)screening visit (Visit 1) then this will be used instead.

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 finalised before breaking the randomisation code.

Any changes from the statistical analyses planned in this clinical trial protocol 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 of missing values for the primary endpoint are described in Section 14.3.8.

For other continuous endpoints for which a MMRM analysis will be used it will be assumed that data is missing at random within each treatment group. The missing data will be predicted by the MMRM model.

For the categorical endpoints for which a CMH test will be used, subjects with missing data will be considered as non-responders and their missing values will be imputed using NRI.

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

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

A supplementary estimand, 'pandemic-modified composite', is introduced for analysis of the primary endpoint to address permanent discontinuation of IMP due to the pandemic as an intercurrent event. Details are described in Section 14.3.8.

Interruption of IMP administration during the treatment period (Weeks 0–16) is not considered as an intercurrent event if only 1 full dose (450 mg) is missed. Observed data from subjects missing more than one dose will be 'treated as missing'. The causal relationship of permanent discontinuation of IMP related to the pandemic will be recorded in the eCRF.

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.

Observed data after permanent discontinuation of IMP related to the pandemic will be 'treated as missing' and imputed assuming MAR. Similarly, missing data and/or initiation of rescue treatment related to the pandemic will be imputed assuming MAR.

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 Section 14.3.7. For the primary analysis of estimands, details of the analysis 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 randomised subjects by last visit attended and by treatment group.

A subject disposition summary table will be made including information of number of subjects who were screened, randomised, exposed and who completed the trial, permanently discontinued IMP, and/or were 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 randomised subjects and by treatment group. Presentations of date of birth, age, sex, ethnicity, race, and baseline EASI score by treatment group will be reported for all randomised subjects.

Other baseline characteristics include height, weight, BMI, duration of AD, concurrent diagnoses (from medical history and indications for concomitant medication), concomitant medication, and previous AD treatments.

14.3.6 Exposure and treatment compliance

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

The cumulated dose administered to each subject will be determined and summarised descriptively. For subjects who withdraw from the trial, are lost to follow-up, or permanently discontinue IMP, their cumulated dose will be calculated up until the time of withdrawal/permanent discontinuation of IMP/loss to follow-up.

Treatment compliance will be presented for the safety analysis set per treatment group as the percentages of missed IMP doses.

14.3.7 Testing strategy

This is a phase 2a trial with the primary objective to investigate efficacy of LEO 138559. For the primary endpoint, change in EASI score from baseline to Week 16, the statistical analysis will be controlled by 2-sided alpha value of 5%. There will be no adjustment for the multiple testing of primary and secondary endpoints, all p-values will be considered nominal.

14.3.8 Analysis of primary endpoint

A primary and 3 supplementary estimands will be defined for the primary endpoint to ensure that occurrence of intercurrent events is taken into account (Panel 12).

Panel 12: Objective and estimands for primary endpoint

Objective	Estimands					Endpoint
	Estimand type (Primary/ Supplementary)	Comparison groups	Interpretation of endpoint	Intercurrent events and strategy	Population level summary	
Primary objective To compare the efficacy of LEO 138559 with placebo in subjects with moderate to severe AD.	Primary	Dose of LEO 138559 450 mg Q2W vs. placebo.	Change in EASI from baseline to Week 16 as if all subjects adhered to the treatment regimen, i.e., they did not permanently discontinue IMP and did not use rescue treatment before Week 16 (Section 14.3.8.1).	Events: Permanent discontinuation of IMP, initiation of rescue treatment Strategy: 'Hypothetical'.	Difference in mean change in EASI from baseline to Week 16.	**Primary endpoint** Change in EASI score from baseline to Week 16.
	First supplementary		Change in EASI from baseline to Week 16 without intercurrent events (Section 14.3.8.2).	Events: Permanent discontinuation of IMP, initiation of rescue treatment Strategy: 'Composite'.		
	Second supplementary		Change in EASI from baseline to Week 16 without intercurrent events and as if COVID-19 pandemic did not happen (Section 14.3.8.3).	Events: Permanent discontinuation of IMP due to non-pandemic-related factors, permanent discontinuation of IMP due to pandemic-related factors, initiation of rescue treatment Strategy: 'Pandemic-modified composite'.		
	Third supplementary		Change in EASI from baseline to Week 16 regardless of intercurrent events (Section 14.3.8.4).	Events: Permanent discontinuation of IMP, initiation of rescue treatment Strategy: 'Treatment policy'.		

Abbreviations: AD = atopic dermatitis; COVID-19 = coronavirus disease 2019; EASI = Eczema Area and Severity Index; IMP = investigational medicinal product; Q2W = every second week.

The following intercurrent events are considered to affect the interpretation of the estimated treatment effects:

- Initiation of rescue treatment: This event occurs when a subject initiates rescue treatment. This event is disallowed during the first 4 weeks of treatment but can occur from week 4 at the discretion of the investigator. The timing of the event will be taken 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. If rescue treatment is initiated before week 4, the subject will be withdrawn from the trial.
- Permanent discontinuation of IMP independent 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, at the discretion of the investigator or the sponsor, or if the subject is lost to follow-up. The timing of the event will be taken as the date of permanent discontinuation of IMP recorded in the eCRF.
- 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; not attributed to lack of efficacy or randomised 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 a *hypothetical strategy* which attempts to quantify the effect of treatment, in the hypothetical situation, where one or more intercurrent events do not occur. In this context, an intercurrent event refers to a post-randomisation event that either precludes the existence of or affects the interpretation of the measurements of the endpoint e.g., permanent discontinuation of IMP.

This primary estimand evaluates the treatment difference in change in EASI score from baseline to Week 16 as if all subjects adhered to the treatment regimen, i.e., they did not discontinue IMP permanently and no rescue treatment was made available before Week 16. Data collected after permanent discontinuation of IMP or after initiation of rescue treatment will not be included in the analysis, but will be ‘treated as missing’ and imputed assuming

MAR. Similarly, for subjects who experience a pandemic-related intercurrent event prior to Week 16, observed data at Week 16 will be 'treated as missing' and imputed assuming MAR.

If data is missing at Week 16 due to a non-pandemic-related intercurrent event, the data will be imputed using MI (100 iterations) assuming MAR within each treatment group and whether the subject has experienced a non-pandemic-related intercurrent event. Within a given treatment group, observed data from subjects not experiencing an intercurrent event will be used to impute missing data for subjects who experience an intercurrent event.

Missing data or data 'treated as missing' at Week 16 due to the pandemic will be imputed using MI assuming MAR within treatment group using data from subjects who have not experienced an intercurrent event.

For each of the 100 complete datasets, the change in EASI score from baseline to Week 16 will be analysed using an ANCOVA model adjusted for treatment, region, baseline EASI score, and baseline disease severity. The pooled estimate of the difference in the LS-mean change from baseline, along with the associated 95% CIs and nominal p-values will be presented based on applying Rubin's rules to the estimates and standard errors from the ANCOVA analysis of the imputed datasets.

14.3.8.1.1 Sensitivity analysis for primary estimand

The primary estimand will be analysed using a MMRM on the post-baseline responses up to Week 16 including treatment, visit, interaction between treatment and visit, region and baseline disease severity as factors and adjusting for baseline EASI score as covariate. The model will use an unstructured covariance matrix, Kenward-Roger approximation to estimate denominator degrees of freedom. This model assumes that data is missing at random within each treatment group and the model will be used to predict missing data. The estimates will be presented with nominal p-values and 95% CI at each visit.

14.3.8.2 First supplementary estimand

A first supplementary estimand will use *composite strategy* to handle intercurrent events. A composite strategy accounts for the occurrence of intercurrent events, through the definition of a suitable composite endpoint, whose components include the aforementioned intercurrent events, as well as the endpoint of interest.

The first supplementary estimand for the primary endpoint is the treatment difference in change in EASI score from baseline to Week 16 as if initiation of rescue treatment or permanent discontinuation of IMP did not happen. For subjects who received rescue treatment

or who have permanently discontinued IMP prior to the endpoint of interest, observed data after the intercurrent events will be considered non-response by using LOCF. Similarly, missing data for subjects who do not attend the visit for the endpoint of interest and do not experience an intercurrent event prior to this visit will be imputed as LOCF.

The change in EASI score from baseline to Week 16 will be analysed using an ANCOVA model adjusted for treatment, region, baseline EASI score, and baseline disease severity. The difference in the LS-mean change from baseline between the treatment groups will be presented along with the corresponding 95% CI and nominal p-value.

14.3.8.2.1 Sensitivity analysis for the first supplementary estimand

For subjects who received rescue treatment or who have permanently discontinued IMP prior to the endpoint of interest, observed data after the intercurrent events will be considered non-response by using WOCF including the baseline value. Similarly, missing data for subjects who do not attend the visit for the endpoint of interest and do not experience an intercurrent event prior to this visit will be imputed as WOCF. The same ANCOVA model described for the primary analysis of the primary estimand will be used.

14.3.8.3 Second supplementary estimand

A second supplementary estimand will use a *pandemic-modified composite strategy*. The strategy follows a composite strategy for intercurrent events independent of the COVID-19 pandemic.

The second supplementary estimand for the primary endpoint is the treatment difference in change in EASI score from baseline to Week 16 without initiation of rescue treatment or permanent discontinuation of IMP and as if the COVID-19 pandemic did not happen. For subjects who experience non pandemic-related intercurrent events prior to the endpoint of interest, observed data after the intercurrent events will be considered non-response by using LOCF. For subjects who experience a pandemic-related intercurrent event prior to the endpoint of interest, observed data after the event will be ‘treated as missing’ and imputed assuming MAR.

For imputation purposes, data available from all subjects will be used, but excluding individual subject data captured after the intercurrent events.

The procedure for imputing values will be implemented in a 2-step procedure, where all missing or ‘treated as missing’ data related to pandemic will be imputed using MI (100 iterations) assuming MAR within treatment groups. Once the 100 complete data sets have

been generated by MI, LOCF imputation of relevant data points not affected by the pandemic will be applied according to the rules described above.

For each of the 100 complete datasets, the change in EASI score from baseline to Week 16 will be analysed using an ANCOVA model including treatment, region, and baseline disease severity as factors and adjusting for baseline EASI score as covariate. The pooled estimate of the difference in the LS-mean change from baseline, along with the associated 95% CIs and nominal p-values will be presented based on applying Rubin's rules to the estimates and standard errors from the aforementioned ANCOVA analysis of the imputed datasets.

14.3.8.4 Third supplementary estimand

A third supplementary estimand will use a *treatment policy strategy* which attempts to quantify the effect of the decision to treat subjects with the randomised treatment, thus ignoring the occurrence of intercurrent events. Data collected for the primary endpoint are used regardless of whether an intercurrent event (independent of the pandemic) occurred. Data collected after an event related to the pandemic will be 'treated as missing' and imputed assuming MAR.

This supplementary estimand will evaluate the treatment difference in change in EASI score from baseline to Week 16 regardless of permanent discontinuation of IMP or initiation of rescue treatment and as if the COVID-19 pandemic did not happen. Observed data will be used in the analysis, including the data observed after the occurrence of non-pandemic-related intercurrent events. For subjects who experience a pandemic-related intercurrent event prior to Week 16, observed data at Week 16 will be 'treated as missing' and imputed assuming MAR.

If data is missing at Week 16 due to a non-pandemic-related intercurrent event, the data will be imputed using MI (100 iterations) assuming MAR within each treatment group and whether the subject has experienced a non-pandemic-related intercurrent event. Within a given treatment group, observed data from subjects not experiencing an intercurrent event will be used to impute missing data for subjects who experience an intercurrent event.

Missing data or data 'treated as missing' at Week 16 due to the pandemic will be imputed using MI assuming MAR within treatment group using data from subjects who have not experienced an intercurrent event.

For each of the 100 complete datasets, the change in EASI score from baseline to Week 16 will be analysed using an ANCOVA model adjusted for treatment, region, baseline EASI

score, and baseline disease severity. The pooled estimate of the difference in the LS-mean change from baseline, along with the associated 95% CIs and nominal p-values will be presented based on applying Rubin's rules to the estimates and standard errors from the ANCOVA analysis of the imputed datasets.

Panel 13 presents an overview of how observed and missing data will be handled according to the intercurrent events for the analyses of estimands.

Panel 13: Handling of intercurrent events and analyses of estimands for the primary endpoint

Events	Data observed or missing	Estimand strategy			
		Primary: 'Hypothetical'	**First supplementary: 'Composite'**	**Second supplementary: 'Pandemic modified composite'**	**Third supplementary: 'Treatment policy'**
Initiation of rescue treatment[a]	Observed	MI (MAR)	LOCF	LOCF	Used
	Missing	MI (MAR)	LOCF	LOCF	MI (MAR)
Permanent discontinuation of IMP **independent of** the pandemic	Observed	MI (MAR)	LOCF	LOCF	Used
	Missing	MI (MAR)	LOCF	LOCF	MI (MAR)
Permanent discontinuation of IMP **related to** the pandemic	Observed	Treated as missing, MI (MAR)	LOCF	Treated as missing, MI (MAR)	Treated as missing, MI (MAR)
	Missing	MI (MAR)	LOCF	MI (MAR)	MI (MAR)
No intercurrent events	Observed	Used	Used	Used	Used
	Missing **independent of** the pandemic	MI (MAR)	LOCF	LOCF	MI (MAR)
	Missing **related to** the pandemic	MI (MAR)	LOCF	MI (MAR)	MI (MAR)

Abbreviations: COVID-19 = coronavirus disease 2019; IMP = investigational medicinal product; LOCF= last observation carried forward; MAR = missing at random; MI = multiple imputation.

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

14.3.9 Analysis of secondary endpoint

Analysis of the secondary endpoint

- Number of treatment-emergent adverse events from baseline to Week 16 per subject.

is described in Section 14.3.14.1 in details.

14.3.10 Analysis of exploratory efficacy endpoints

Binary endpoints

The following 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.

will be analysed using CMH test stratified by region and baseline disease severity. Subjects who received rescue treatment prior to the Week 16 visit or permanently discontinued IMP or have missing data will be considered as non-responders. Additionally, responder rates will be summarised descriptively at each visit by treatment group.

Time-to-event endpoints

The endpoints;

- Time to having a decrease in EASI of at least 50% (EASI 50) between baseline and Week 16.
- Time to having a decrease in EASI of at least 75% (EASI 75) between baseline and Week 16.
- Time to having a decrease in EASI of at least 90% (EASI 90) between baseline and Week 16.
- Time to initiation of TCI or TCS rescue treatment between baseline and Week 16.

will be analysed according to Gray's test, stratified by region and baseline disease severity. Gray's test accounts for the occurrence of the competing risks, permanent discontinuation of IMP and initiation of rescue treatment. Inference will be based on the estimated cumulative incidence of achieving the endpoint derived from the Aalen-Johansen estimator. The

estimated cumulative incidence functions will be presented by treatment group along with 95% confidence bands.

14.3.11 Analysis of patient-reported outcomes

Continuous endpoints

The following endpoints;

- Change in Worst Daily Pruritus NRS (weekly average) from baseline to Weeks 1, 2, 4, 8, 12, and 16.
- Change in POEM score from baseline to Week 16.
- Change in DLQI from baseline to Week 16.

will be summarised descriptively at each visit by treatment group and will be analysed using a MMRM model including treatment, visit, interaction between treatment and visit, region and baseline disease severity as factors and adjusting for baseline value for the endpoint of interest as covariate. The model will use an unstructured covariance matrix, Kenward Roger approximation to estimate denominator degrees of freedom. For these endpoints, data collected after permanent discontinuation of IMP or after initiation of rescue treatment will not be included in the analysis but will be 'treated as missing'. This model assumes that data is missing at random within each treatment group. The estimates will be presented with nominal p-values and 95% CI at each visit.

Binary endpoints

The following endpoints;

- Having a decrease in Worst Daily Pruritus NRS (weekly average) of ≥3 points from baseline at Weeks 1, 2, 4, 8, 12, and 16, assessed separately.
- Having a decrease in Worst Daily Pruritus NRS (weekly average) of ≥4 points from baseline at Weeks 1, 2, 4, 8, 12, and 16, assessed separately, among subjects with a baseline Worst Daily Pruritus NRS ≥4 points.

will be summarised descriptively at each visit by treatment group and will be analysed using the same CHM test described in Section 14.3.10 for binary endpoints.

Time-to-event endpoints

The endpoints;

- Time to reduction of Worst Daily Pruritus NRS (weekly average) of ≥3 points between baseline and Week 16.
- Time to reduction of Worst Daily Pruritus NRS (weekly average) of ≥4 points between baseline and Week 16 among subjects with a baseline Worst Daily Pruritus NRS ≥4 points.

will be summarised descriptively at each visit by treatment group and will be analysed using the same analysis method described in Section 14.3.10 for time-to-event endpoints.

14.3.12 Analysis of pharmacodynamics

For the following endpoints;

- Change in expression of AD disease biomarkers in serum from baseline to Week 16.
- Change in expression of AD disease biomarkers in skin from baseline to Week 16.

explorative analyses will be performed for the total population as well as by baseline disease severity.
A summary of the results will be included in the CTR if the results are available in time for this. The full set of biomarker results will be reported in an addendum to the CTR.

14.3.13 Exploratory analyses

Descriptive statistics of BSA score (absolute and change from baseline) will be summarised at each visit by treatment group. Additional exploratory analyses will be described in the SAP and will be performed 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 course of the trial according to the MedDRA. AEs will be presented by preferred term and primary SOC.

Treatment-emergent AEs will be summarised; however, all AEs recorded during the course of 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 starting 18 weeks after the last dose of IMP. The tabulations described in the following will only include the treatment-emergent events. In each of the tabulations, AEs are defined by MedDRA preferred terms within primary SOC.

AEs will be summarised 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 for all AEs, SAEs, related AEs, AESIs, and AEs leading to withdrawal from trial and/or permanent discontinuation of IMP. 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 AEs will be tabulated by treatment group from baseline to Week 16, from baseline to Week 32, and from Week 17 to Week 32.

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 IMP administration. No narratives will be given.

14.3.14.2 Vital signs and physical examination

The change in vital signs (blood pressure, pulse, and body temperature) from baseline to each relevant visit will be summarised 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 ECG

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

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

14.3.14.4 Clinical laboratory evaluation

The change in each of the laboratory parameters from baseline to each visit will be summarised 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.

14.3.14.5 Anti-drug antibodies

For the endpoint

- Having a positive ADA response at Weeks 0, 4, 8, 12, 16, 32, assessed separately.

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

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

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

For ADA, all subjects with titre information will be listed. Graphical presentations may be performed.

14.3.15 Analysis of pharmacokinetics

The endpoint

- Serum concentration of LEO 138559 at Weeks 0, 1, 2, 4, 6, 8, 10, 12, 14, 16, 32, assessed separately.

will be evaluated based on the PK analysis set. LEO 138559 serum concentrations will be listed and summarised by visit.

14.3.16 Interim analysis

The trial will be unblinded once all randomised subjects have completed the Week 16 visit. All pre-specified analyses will be based on the data lock point date of the last subject's Week 16 visit. The CTR will include all data from the trial including data from the safety follow-up period.

A written plan (trial blinding plan) detailing the blinded/unblinded staff for the interim analysis will be prepared before FSFV.

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Appendix 1: Definitions of adverse events and serious adverse events

Adverse event definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (60)

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavourable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures*.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 11.4.5.2).

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 hospitalisation or prolongation of existing hospitalisation*.
- 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 hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, and convulsions that do not result in hospitalisation, development of drug dependency, or drug abuse.

*Hospitalisation 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.

Hospitalisation 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.

Hospitalisation 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.

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

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

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

Definition of adverse events of special interest

An AESI (serious or non-serious) is one of scientific and medical concerns specific to the sponsor's product or programme, for which ongoing monitoring may be appropriate. Such an event might warrant further investigation in order to characterise 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) might also be warranted.

AESIs are described in Sections 13.6.1.

Appendix 2: Classification of adverse events

Severity

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

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

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

Causality

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

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.

Serious adverse events

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

Appendix 3: Trial governance considerations

Appendix 3A: Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki (38) and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines (61).
- Current version of applicable International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines (54).
- EU General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

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

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

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

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

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the local IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the trial at the trial site and 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 emphasise that participation in the clinical trial is voluntary and that the subject may withdraw from the clinical trial at any time and for any reason. All subjects will be given an opportunity to ask questions and will be given sufficient time to consider before consenting.

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

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

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

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

Appendix 3C: Subject and data confidentiality

This clinical trial protocol as well as all other information, data, and results relating to this clinical trial and/or to the IMP is confidential information of LEO 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 authorised 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 (for example race, ethnicity, age, gender, health condition, medical history, test results, etc.) which shall be collected as part of the clinical trial and processed during and after trial completion.

Personal data collected as part of the clinical trial will be transferred to/from the institution/investigator, LEO Pharma, and third parties acting on behalf of LEO Pharma.

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

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

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

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

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

Source data 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.

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.
- A statement from the investigator to verify that each of the eligibility criteria were met and documented.
- Randomisation code number.
- The fact that the subject is participating in a clinical trial in AD including treatment with LEO 138559 or placebo for 16 weeks.
- Other relevant medical information.

Trial monitoring

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

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

In addition to on-site monitoring, pre-specified trial data will undergo central monitoring as specified in the trial's data review plan.

In order to perform their role effectively, CRAs (blinded or unblinded) and persons involved in quality assurance and inspections will need direct access to source data, for example, medical records, laboratory reports, appointment books, etc. based on the assignment. If the electronic medical record does not have a visible audit trail, the investigator must provide the applicable CRA (blinded or unblinded) 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 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 authorised by the investigator will enter subject data into eCRFs. 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 authorised 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 applicable CRA (blinded or unblinded), sponsor's medical expert, or the data manager. All queries will be raised electronically within the electronic data capture system. This systematic validation will ensure that a clean and consistent database is provided for the statistical analysis.

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

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.

Software used
CDISC controlled terminology version 06-Nov-2020 or newer was 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 (54). Essential trial documents must be stored until LEO Pharma informs the investigator that the documents are no longer to be retained, or longer if required by local regulations.

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

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

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

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

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

Appendix 3E: Registration, reporting, and publication policy

Trial disclosure

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

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

Results of this clinical trial will be posted on 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 fulfil 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 anonymised data from this trial for further research according to the principles outlined by the European Federation of Pharmaceutical Industries and Associations (EFPIA) (62). 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 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

Not applicable

Appendix 3I: Trial and trial site closure

Premature termination of trial or trial site

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

If a clinical trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. As specified by applicable

regulatory requirements, the investigator or LEO Pharma must promptly inform IRB/IECs and provide a detailed written explanation. Relevant competent authorities must be informed.

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

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

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

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

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

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

Appendix 3J: Responsibilities

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

The national coordinating investigators are responsible for national issues relating to the clinical trial as agreed to in a national coordinating investigator agreement.

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

Appendix 4: AAD Consensus Criteria for the diagnosis of AD

From Eichenfield, L. F. (2004). "Consensus guidelines in diagnosis and treatment of atopic dermatitis." Allergy 59(s78): 86-92.

AD is best viewed as a syndrome. Clinical findings that define this syndrome and clinical criteria of AD include the following:

A. Essential features (must be present):
    1. Pruritus
    2. Eczema (acute, subacute, chronic)
        a) Typical morphology and age-specific patterns*
        b) Chronic or relapsing history

*Patterns include: (i) facial, neck, and extensor involvement in infants and children; (ii) current or prior flexural lesions in any age group; (iii) sparing of groin and axillary regions.

B. Important features (seen in most cases, adding support to the diagnosis)
    1. Early age at onset
    2. Atopy
        a. Personal and/or family history
        b. IgE reactivity
    3. Xerosis

C. Associated features (these clinical associations help to suggest the diagnosis of AD but are too nonspecific to be used for defining or detecting AD for research or epidemiologic studies):
    1. Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
    2. Keratosis pilaris/hyperlinear palms/ichthyosis
    3. Ocular/periorbital changes
    4. Other regional findings (e.g., perioral changes/periauricular lesions)
    5. Perifollicular accentuation/lichenification/prurigo lesions

Exclusionary conditions: It should be noted that a diagnosis of AD depends on excluding conditions such as scabies, seborrheic dermatitis, allergic contact dermatitis, ichthyoses, cutaneous lymphoma, psoriasis, and immune deficiency diseases.

Appendix 5: Guidance for anaphylaxis diagnosis

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

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

Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:

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

AND AT LEAST ONE OF THE FOLLOWING:

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

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

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

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

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

Appendix 6: Country-specific requirements

Not applicable

Appendix 7: Short version and justification for eligibility criteria

Inclusion criteria		
No.	**Short version**	**Justification**
1	Signed and dated informed consent has been obtained prior to any protocol-related procedures.	To ensure compliance with Declaration of Helsinki (38) and GCP.
2	18-64 years old (both included) at screening.	To ensure only adults are included given the early stage of development. Subjects older than 65 years are excluded to ensure safety of subjects by decreasing the risk of enrolling subjects who may be at increased risk of severe COVID-19 infection.
3	Diagnosis of AD [as defined by the AAD Consensus Criteria (1) and Appendix 4] that has been present for ≥1 year prior to screening.	To ensure that the subject has AD.
4	Subjects who have a recent history (within 6 months before screening) of inadequate response to treatment with topical medication, or for whom topical treatments are otherwise medically inadvisable.	To ensure that the subject is a candidate for systemic treatment with LEO 138559.
5	EASI score ≥12 at screening and ≥16 at baseline.	To ensure that the subject has a severity of disease that makes assessment of improvement possible.
6	vIGA-AD score ≥3 at screening and baseline.	To ensure that the subject has a severity of disease that makes assessment of improvement possible.
7	Body surface area (BSA) of AD involvement ≥10% at screening and baseline.	To ensure that the subject has a BSA involvement that makes assessment of improvement possible.
8	Worst Daily Pruritus NRS (weekly average) of ≥3 points at baseline.	To ensure that the subject has a severity of itch that makes assessment of improvement possible.
9	Subject agrees to apply an emollient twice daily (or more frequently, if needed) to AD lesional and non-lesional skin for at least 7 days before baseline.	To provide subjects with baseline standard of care therapy.

10	A woman of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline.	For the safety of the unborn/newborn child.
11	A woman of childbearing potential must use a highly effective form of birth control throughout the trial and at least for 18 weeks after last administration of IMP.	For the safety of the unborn/newborn child.

Exclusion criteria		
No.	**Short version**	**Justification**
1	Active dermatologic condition that could confound the diagnosis of AD or interfere with assessment of the treatment.	To exclude conditions that are likely to interfere with the assessment of severity of AD.
2	Previously randomised in this clinical trial.	To ensure integrity and validity of the trial data due to the possibility of duplicate subject entries.
3	Current participation in any other interventional clinical trial.	To ensure safety of subjects and ensure lack of confounding of measurements (e.g., efficacy, PK, and PD).
4	Treatment with systemic immunosuppressive/immunomodulating medication, immunoglobulin/blood products, or phototherapy within 4 weeks or 5 half-lives prior to randomisation, whichever is longer.	To not interfere with efficacy assessments.
5	Treatment with biologics within 5 half-lives (if known) or 16 weeks prior to randomisation, whichever is longer.	To not interfere with efficacy assessments.
6	Treatment with TCS, TCI, topical PDE-4 inhibitor, or other topical prescription treatments within 1 week prior to randomisation.	To not interfere with efficacy assessments.
7	Treatment with a live (attenuated) vaccine within 12 weeks prior to randomisation.	As LEO 138559 could potentially interact with this.

8	History of malignancy within 5 years prior to randomisation, apart from nonmetastatic BCC, SCC of the skin, or cervical carcinoma in-situ, considered cured by the standard of care.	To ensure safety of subjects.
9	Clinically significant active chronic or acute infection requiring systemic treatment within 4 weeks prior to randomisation that may compromise the safety of the subject.	To ensure safety of subjects given the potential increased risk of infections of the skin with LEO 138559.
10	Skin infection within 1 week prior to randomisation.	To ensure safety of subjects given the potential increased risk of infections of the skin with LEO 138559.
11	Current or recent (within 2 years prior to randomisation) gastrointestinal ulcers.	To ensure safety of subjects given the potential increased risk of impaired wound healing of the intestine with LEO 138559.
12	History of any of the following: anaphylaxis, immune complex disease, pancreatic disease, inflammatory bowel disease, or known or suspected history of immunosuppressive disorder.	Anaphylaxis: To ensure safety of subjects given the potential increased risk of anaphylaxis and serious allergic reactions after administration of foreign proteins. Immune complex disease: To ensure safety of subjects given the potential increased risk that antibody-antigen complexes can accumulate and cause a Type III allergic reaction. Pancreatic disease: To ensure safety of subjects given the potential increased risk of impaired wound healing of pancreas with LEO 138559. Inflammatory bowel disease: To ensure safety of subjects given the potential increased risk of impaired wound healing of intestine with LEO 138559. Known or suspected history of immunosuppressive disorder: To ensure safety of subjects given the potential increased risk of infections of the skin, lung, and intestines with LEO 138559.
13	Known or suspected hypersensitivity to any component(s) of the IMP.	To ensure safety of subjects.
14	Presence of hepatitis B or C infection at screening. These are defined as: 1) Positive hepatitis C Ab, or 2) Positive HBsAg, or 3) Negative anti-HBs Ab AND positive anti-HBc Ab.	To ensure safety of subjects given the potential increased risk of infections with LEO 138559.

15	History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.	To ensure safety of subjects given the potential increased risk of infections with LEO 138559.
16	Subject has a positive or indeterminate *Mycobacterium tuberculosis* IFN-γ release assay test or a positive purified protein derivative PPD test at screening.	To ensure safety of subjects given the potential increased risk of infections of the lung with LEO 138559.
17	Current diagnosis of diabetes.	To ensure safety of subjects by decreasing the risk of enrolling subjects who may be at increased risk of severe COVID-19 infection.
18	Serious heart conditions (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and/or pulmonary hypertension).	To ensure safety of subjects by decreasing the risk of enrolling subjects who may be at increased risk of severe COVID-19 infection.
19	Chronic lung diseases (e.g., chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and/or cystic fibrosis).	To ensure safety of subjects by decreasing the risk of enrolling subjects who may be at increased risk of severe COVID-19 infection.
20	Moderate to severe asthma [as defined by GINA guidelines (42)].	To ensure safety of subjects by decreasing the risk of enrolling subjects who may be at increased risk of severe COVID-19 infection.
21	Obesity (BMI ≥35).	To ensure safety of subjects by decreasing the risk of enrolling subjects who may be at increased risk of severe COVID-19 infection.
22	Subject has laboratory abnormalities that, in the opinion of the investigator, will prevent the subject from completing the trial or interfere with the analysis of results.	To ensure safety of subjects.
23	Subject is pregnant or lactating.	For the safety of the unborn/newborn child.
24	Subject has a history of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.	To ensure safety of the subjects, and integrity and validity of the trial data.
25	Employees of the trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.	To ensure integrity of trial data.
26	Any disorder at screening and/or baseline, which is not stable in the opinion of the investigator	To ensure safety of the subjects, and integrity and validity of the trial data.

27	Any significant abnormal finding at baseline and/or screening which may in the opinion of the investigator	To ensure safety of the subjects, and integrity and validity of the trial data.
28	Treatment with any non-marketed drug substance within the last 4 weeks or 5 half-lives prior to randomisation, whichever is longer.	To ensure safety of subjects and ensure lack of confounding of measurements (e.g., efficacy, PK, and PD).
29	Subjects who are legally institutionalised.	To ensure compliance with Declaration of Helsinki (38).
30	Positive SARS-CoV-2 PCR test at screening.	To ensure safety of subjects and trial site staff.

Appendix 8: Contact list

Contact details for the CPM, National Lead CRAs, CRAs (blinded and unblinded), 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
[redacted]
Germany

Appendix 9: COVID-19 pandemic contingency plan

Without compromising subject and site staff safety as well as trial integrity, it is expected that all efforts will be made to ensure subject attendance to the planned trial visits and thereby ensure the conduct of important safety and efficacy assessments.

As protective/preventive measures to be taken in the context of the COVID-19 pandemic can differ across countries and regions, no general instructions from the sponsor can be provided and the investigators will be trusted to take appropriate action. This includes but is not limited to complying with recommendations and regulations issued by their local health authorities, the increase of protective safety and hygiene measures (e.g., wearing mask, disinfecting hands, social distancing) for both subject and site staff, and the frequent monitoring of the subject's health.

To minimise subject exposure to COVID-19 in public transportation and public areas, 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 due to preventive measures issued by local health authority(ies) or site obligations, the affected site(s) will postpone screening and randomisation of subjects until on-site visits can be conducted again.

Safety monitoring is an obligation of LEO Pharma and in case the subject, due to local restrictions, is prevented from coming to the trial site, the investigator can convert on-site visits into phone visits for the primary purpose of safety monitoring. At a phone visit, the following data may be collected:

- AEs.
- Concomitant medication and concurrent procedures.
- Urine pregnancy test. Women of childbearing potential will be provided with urine pregnancy tests, if needed. The subject will take the test at home and inform the investigator about the result over the phone.
- POEM and DLQI collected on the web-based solution by remote transfer to the vendor.

The phone visits must not be used for conducting the investigator's assessments of efficacy.

If on-site visits are not possible, it will be at the discretion of the investigator if clinical laboratory samples or a serum pregnancy test are necessary to ensure subject safety.

A subject testing positive for COVID-19 (test taken at their own initiative) between screening (at the earliest Week -4) and washout (Week -1) may be rescreened once if the screening period does not exceed 28 days in total (see Section 8.4). A subject testing positive during the washout period (Week -1 to Week 0) must be withdrawn from the trial. A subject testing positive for COVID-19 after randomisation may be temporarily discontinued from IMP. IMP treatment may be reinstituted at the investigator's discretion.

In general, in the context of the COVID-19 pandemic, in case site visits will not be possible, more frequent telephone contacts between site staff and subjects should take place to closely monitor subject safety and the status of subject participation in the trial and to provide guidance to the subject as to what they are required to do in a remote setting to maximise data integrity and quality.

Reporting in eCRF

It will be recorded in the eCRF if a visit or an assessment was conducted remotely or if it was not conducted. If it was not conducted, it will be recorded if this was due to the COVID-19 pandemic. Telephone contacts and occurrence of unscheduled visits if allowed to take place during the pandemic will also be recorded. It will be recorded if the telephone contact or unscheduled visits were due to the pandemic.

Appendix 10: Protocol amendment history

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

Amendment 2 (17-Nov-2021)
This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union 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 for this protocol amendment is to remove the capping specified for each AD disease severity group (moderate defined as EASI <21 and severe defined as EASI ≥21) in Sections 7.1 and 12.1.

In the protocol a capping was introduced to ensure enrolment of enough subjects with a high unmet need (defined as severe subjects with a baseline EASI score ≥21). This was originally described in the protocol in Section 12.1: 'The minimum limit for inclusion of 50% of subjects with 'stratum B' at baseline has been chosen to ensure inclusion of a suitable proportion of subjects representative of the target population that experiences a high unmet need for AD treatments.' This capping was further addressed in the protocol in Section 7.1 stating that each stratum ('stratum A' defined as having EASI <21 and 'stratum B' defined as having EASI ≥21) will comprise exactly 26 subjects randomised, equivalent to 50% of the total sample size.

During trial conduct it has become clear that the screening process of trying to reach the exact distribution as original stated in Section 7.1 is more complex than anticipated. However, it has also become clear that severe subjects with a baseline EASI score ≥21 represent more than 50% of subjects fulfilling the eligibility criteria, and therefore the initial aim to include sufficient subjects with an unmet need is no longer of concern.

Removing the capped enrolment does not affect the total number of subjects, statistical analysis methods or interpretation of the trial results, and has no impact on patient safety, thus no impact on the scientific value or integrity of the trial.

All changes to the protocol are presented in the summary of changes table below except for a few minor editorial changes (e.g., spelling errors).

Summary of changes

Section no. and name	Description of change	Brief rationale
Section 1 Protocol synopsis, Section 2 Trial identification under EudraCT number	NCT number added. ~~Pre~~ IND	Editorial.
Section 1 Protocol synopsis, Section 8.3 Exclusion criteria, no. 10 and Appendix 7 Short version and justification for eligibility criteria	Skin infection within 1 week prior to ~~the baseline visit~~ **randomisation.**	To be more specific and consistent.
Section 4 Schedule of trial procedures, footnote o)	o) Relevant concomitant medications / concurrent procedures should be included from 3 months prior to ~~baseline (Day 1)~~ **screening** until end of trial (Week 32).	To align with Section 9.6.
Section 7.1 Overall trial design	Randomisation will be stratified by baseline disease severity. One stratum, 'stratum A', will be defined as having EASI <21 and the other stratum, 'stratum B', will be defined as having EASI ≥21. ~~Each stratum will comprise exactly 26 subjects randomised, equivalent to 50% of total sample size.~~ IRT will be used to control randomisation and stratification factors.	To remove the capping for both strata. However, stratified randomisation to assure that treatment groups are balanced will be maintained.
Section 9.3 Treatment assignment	~~Subjects eligible on inclusion/exclusion criteria at baseline may be prevented from being randomised into the trial due to the applied capping limitation in baseline severity (as described in Section 8.2).~~	This has been deleted as the capping for both strata is removed (see above).
Section 9.5 Rescue treatment	~~If a subject receives rescue treatment with any TCS/TCI before Week 4, super potent TCS (e.g., clobetasol propionate 0.05% cream) between Week -1 and Week 16, or systemic rescue treatment (besides systemic antihistamines and/or anti-infectives) at any point during the trial between Week -4 (or 5 half-lives, whichever is longer) and Week 32, treatment with IMP will be discontinued, and the subject will be withdrawn from the trial.~~	For readability and to align Section 9.5 with Section 10.1.

Section no. and name	Description of change	Brief rationale
	However, treatment with IMP will be discontinued if a subject receives the following treatment: **Rescue treatment with any TCS/TCI before Week 4.** **Super potent TCS (e.g., clobetasol propionate 0.05% cream) between Week -1 and Week 16.** **Systemic rescue treatment (besides systemic antihistamines and/or anti-infectives) at any point during the trial between Week -4 (or from 5 half-lives of Week 0, whichever is longer) and Week 16.**	
Section 10.2.1 Reasons for permanent discontinuation of IMP	In the Reporting in eCRF subsection, 'Death' has been deleted.	Death is captured as an SAE and to align with the eCRF.
Section 11.1 Overview	AEs must be assessed by ~~medically qualified personnel~~ **a physician** (Section 13.2).	Editorial.
Section 11.4.4 ECG	At each visit, the individual measurements as well as the average of 3 consecutive 12-lead resting digital ECG **measurements** will be recorded after the subject has been in supine position for at least 5 minutes. ~~ECG must be measured before any blood samples scheduled at the same visit.~~	In alignment with Section 11.1, the ECG measurements can be done at any time, and not in any pre-specified order.

Section no. and name	Description of change	Brief rationale
Section 12.1 Scientific rationale for trial design	**The combination of randomisation and blinding (Section 9.3.1) minimises the likelihood of allocation bias. The risk of allocation bias is further reduced through the use of central randomisation. The use of randomisation also ensures that baseline factors will not be confounded with treatment. Randomisation within the strata defined by baseline disease severity ('stratum A' [EASI <21] or 'stratum B' [EASI ≥21]) will limit any potential imbalance in the allocation of subjects across baseline disease severity.** ~~Stratified randomisation according to baseline disease severity ("stratum A" [EASI <21] or "stratum B" [EASI ≥21]) will minimise allocation bias and ensure balanced allocation of subjects with "stratum A" vs. "stratum B" at baseline between the treatment groups, thereby minimising baseline confounding. The minimum limit for inclusion of 50% subjects with "stratum B" at baseline has been chosen to ensure inclusion of a suitable proportion of subjects representative of the target population who experiences a high unmet need for AD treatments.~~	The rational for randomisation and blinding has been updated to clarify and be more specific on how to avoid imbalance of allocation of subjects across baseline disease severity and treatment arms. The capping for both strata has been removed (Please refer to change in Section 7.1). However, stratified randomisation to assure that treatment groups are balanced will be maintained.
Section 13.2 Collection of adverse event reports	AEs must be assessed by ~~medically qualified personnel~~ **a physician**. **In the US only, certain AE assessments can be delegated to investigators with other qualifications. However, the diagnosis, seriousness, and causality of the AEs must be assessed by a physician.**	Clarification.
Appendix 1 Definitions of adverse events and serious adverse events	~~Additionally, all malignancies, including skin malignancies, should be reported as SAEs.~~	Editorial.
Appendix 10 Protocol amendment history	Protocol amendment 1, Summary of changes table moved to Appendix 10.	Editorial

Section no. and name	Description of change	Brief rationale
Appendix 10 Protocol amendment history	Addition of a provision to allow rescreening of subjects testing positive for COVID 19 ~~or with an indeterminate tuberculosis test~~ at screening and conditions for rescreening.	Correction to Amendment 1 Summary of changes table.

Abbreviations: please refer to the list of abbreviations.

Amendment 1 (07-May-2021)

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

Overall rationale for the amendment

The purpose of this protocol amendment is to allow for the clarification and addition of eligibility criteria and the inclusion of additional safety assessments. The most important changes to the protocol are summarised in the table below. Additional minor changes, not listed in the table, were included for clarity and consistency.

Summary of changes

Section no. and name	Description of change	Brief rationale
Section 1 Protocol synopsis Section 8.2 Inclusion criteria or Section 8.3 Exclusion criteria Appendix 7 Short version and justification for eligibility criteria	Changes to eligibility criteria: • Inclusion criterion no. 2: 18-64 years old (both included) at ~~baseline~~ **screening**. • Exclusion criterion no. 8: History of malignancy within 5 years prior to randomisation, apart from ~~adequately treated~~ nonmetastatic basal cell carcinoma, squamous cell carcinoma of the skin, or cervical carcinoma in-situ**, considered cured by the standard of care.** • Exclusion criterion no. 16: Subject has a positive **or indeterminate** *Mycobacterium tuberculosis* IFN-γ release assay test or a positive purified protein derivative (PPD) test at screening. Addition of eligibility criterion: • Exclusion criterion no. 30: Positive SARS-CoV-2 PCR test at screening.	To ensure that subjects are at least 18 years at screening when they provide informed consent. To ensure that only subjects considered cured from nonmetastatic basal cell carcinoma, squamous cell carcinoma of the skin, or cervical carcinoma in-situ by the standard of care will be included in the trial. To ensure that only subjects with a negative tuberculosis test at screening will be included in the trial. To increase subject and trial site staff safety.

Section no. and name	Description of change	Brief rationale
Section 4 Schedule of trial procedures Section 11.2.4 Other assessments Section 11.4.5.1 Overview Section 11.4.5.2 Investigator evaluation of laboratory samples	Addition of a SARS-CoV-2 PCR test at screening.	To increase subject and trial site staff safety.
Section 8.4 Screening and screening failures	Addition of a provision to allow rescreening of subjects testing positive for COVID-19 at screening and conditions for rescreening. Rescreening may be allowed after evaluation by the sponsor's medical expert and provided that the screening period does not exceed 28 days in total.	To mitigate potential issues with subject recruitment.
Appendix 9 COVID-19 pandemic contingency plan	Addition of text to clarify actions in case subjects test positive for COVID-19 (test taken at their own initiative) during the screening period. Subjects testing positive between Week -4 and Week -1 may be rescreened under the conditions described in Section 8.4. Subject testing positive between Week -1 and Week 0 will be withdrawn from the trial.	To provide guidance to the investigator and mitigate potential issues with subject recruitment.
Section 4 Schedule of trial procedures	Addition of a clinical chemistry/haematology blood sample at Week 2. Addition of a separate line for IgE analysis.	To increase subject safety. To clarify that hepatitis B, C, and HIV testing will be conducted at screening only and that IgE analysis will be conducted from baseline at the visits indicated in the schedule of trial procedures.
Section 11.1 Overview Panel 6: Sequence of assessments	Grouping of *safety and laboratory assessments*, *PK blood samples*, and *pharmacodynamics* in 1 unique box in the panel and addition of a footnote to explain this.	Because the order in which safety and laboratory assessments, PK blood sampling and pharmacodynamics are conducted does not matter as long as all of the above assessments are conducted after the investigator assessments and before administration of IMP.

Section no. and name	Description of change	Brief rationale
Section 11.4.5.1 Overview	Addition of analytes tested: lactate dehydrogenase and C-reactive protein.	To increase understanding of systemic inflammation.
Section 12.1 Scientific rationale for trial design	Addition of a rationale for the additional dose of IMP given at Week 1. Weekly dosing from Week 0 to Week 2 will allow 75% of the expected steady state exposure to be safely reached already after 3 weeks of treatment.	To clarify the reason for supplementing the Q2W dosing schedule with a dose of IMP at Week 1.
Appendix 3D Record keeping, quality control, and data handling	Change in the trial monitoring subsection and update of the monitoring method. The monitoring will be performed in a systematic, prioritised, risk-based approach, and as a combination of on-site, remote, and centralised monitoring.	To clarify how monitoring will be conducted.

Abbreviations: please refer to the list of abbreviations.