Cover Page

Study title:	A phase 2b, randomized, double-blind, placebo-controlled, multi-site, parallel-group, dose-finding trial to evaluate the efficacy and safety of different doses of subcutaneously administered LEO 138559 in adult subjects with moderate-to-severe atopic dermatitis
LEO Pharma number:	LP0145-2240
NCT number:	NCT05923099
Date:	28-Jun-2024

Updated clinical trial protocol

Trial ID: LP0145-2240

A phase 2b, randomized, double-blind, placebo-controlled, multi-site, parallel-group, dose-finding trial to evaluate the efficacy and safety of different doses of subcutaneously administered LEO 138559 in adult subjects with moderate-to-severe atopic dermatitis.

Phase 2b dose-finding trial

Approval statement, LEO Pharma A/S

The following persons have approved this CTP.

Name, academic degree	Role	Department
[redacted] MD	Vice president	Global Clinical Development
[redacted] MSc Stat	Biostatistics lead	Biostatistics
[redacted] MD, PhD	Medical lead	Medical Department
[redacted] MSc pharm	Clinical operations lead	Global Clinical Operations
Stephan Weidinger, MD	Signatory investigator	External

Title page

Trial ID	LP0145-2240
Protocol title:	A phase 2b, randomized, double-blind, placebo-controlled, multi-site, parallel-group, dose-finding trial to evaluate the efficacy and safety of different doses of subcutaneously administered LEO 138559 in adult subjects with moderate-to-severe atopic dermatitis.
Brief title:	A trial to evaluate the efficacy and safety of different doses of LEO 138559 in adults with moderate-to-severe atopic dermatitis.
Trial phase:	Phase 2b
Compound:	LEO 138559
Indication:	Moderate-to-severe AD
Trial sponsor:	LEO Pharma A/S Industriparken 55, DK 2750 Ballerup, Denmark
Regulatory agency identifier numbers:	Universal trial number: U1111-1286-0955 ClinicalTrials.gov ID: NCT05923099 IND number: 146054 EU CT number: 2022-500777-14 Japanese trial registration number: 2023-1450
Version:	8.0
Approval date:	28-Jun-2024

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP (1), and the applicable regulatory requirement(s).

Protocol amendment summary of changes

Document history

Document	Date	Type of protocol amendment
Amendment 2 (substantial)	28-Jun-2024	Global
Amendment 1 (non-substantial)/GBR-1	05-Feb-2024	Country-specific
Amendment 1 (non-substantial)	13-Nov-2023	Global
Amendment 3 (non-substantial)/CZE-2/DEU-2/ESP-2/ FRA-3/HUN-2/POL-2/ROU-2	05-Oct-2023	Country-specific
Amendment 2 (non-substantial)/FRA-2	28-Sep-2023	Country-specific
Amendment 1 (non-substantial)/CZE-1/DEU-1/ESP-1/ FRA-1/HUN-1/POL-1/ROU-1	16-Sep-2023	Country-specific
Amendment 1 (non-substantial)/JPN-1	12-Jul-2023	Country-specific
Original protocol	04-May-2023	NA

Abbreviations: CZE = Czech Republic; DEU = Germany; ESP = Spain; FRA = France; GBR = United Kingdom; HUN = Hungary; JPN = Japan; NA = not applicable; POL = Poland; ROU = Romania.

Amendment 2 (28-Jun-2024)

This amendment is considered to be substantial based on the criteria set forth in Article 2 (13) of Regulation 536/2014 of the European Parliament and the Council of the European Union or subsequent regulation.

Overall rationale for the amendment

The main purpose of this protocol amendment is to improve the hypothetical estimand to better reflect the underlying trial objective of estimating an effect in a scenario where the subjects do not discontinue IMP or take rescue treatment. Changes to the protocol are summarized in the table below (text added to the protocol is written in **bold**).

Section no. and title	Description of change	Brief rationale
Section 3 Trial objectives, estimands, and endpoints Panel 3 and Panel 4 Section 11.3.7 Estimand strategy Panel 17	Changed description of POEM-related exploratory endpoint: • Change in POEM score **(and individual item scores related to itch and sleep)** from baseline to Week 16.	To evaluate the effect of LEO 138559 on itch and sleep.
Section 3 Trial objectives, estimands, and endpoints Panel 4	Added hypothetical supplementary analysis for continuous endpoints. Changed descriptions of: - Strategy/Intercurrent events for primary estimand for binary endpoints.	For consistency with other changes implemented in Sections 11.3.7 and 11.3.8.

Section no. and title	Description of change	Brief rationale
	- Population level summary for primary estimand for time-to-event endpoints.	
Section 11.3.7 Estimand strategy Panel 16	Added hypothetical supplementary analysis for continuous endpoints. Changed description of handling of missing data.	To improve handling of missing data to better reflect the trial objective.
Section 11.3.7 Estimand strategy Panel 17	Added estimands to be analyzed for continuous endpoints.	To ensure extra quality and robustness of the results.
Section 11.3.7.1 Estimands for continuous endpoints	Added hypothetical supplementary analysis for continuous endpoints.	To ensure extra quality and robustness of the results.
Section 11.3.7.2 Estimands for binary endpoints Section 11.3.7.4 Baseline subgroup estimands	Estimands changed so that permanent discontinuation of IMP due to an AE is considered non-response only if the AE is related to worsening of AD.	To achieve more meaningful definitions of binary endpoints.
Section 11.3.8.1 Analysis of primary estimand for continuous endpoints	Changed handling of the missing data.	To improve handling of missing data to better reflect the trial objective.
Section 11.3.8.2 Analysis of primary estimand for binary endpoints	Changed definition of non-responder.	To make the term 'responder' more meaningful.
Section 11.3.9.1 Analysis of hypothetical supplementary estimand for continuous endpoints	Added section describing analysis of a new supplementary estimand.	To ensure extra quality and robustness of results.
Section 11.3.9.3 Analysis of supplementary estimand for binary endpoints	Changed estimand for the primary analysis.	To introduce a treatment policy estimand for binary endpoints.
Section 12.5.5 Specific requirements for the United Kingdom	Section added to implement changes from Amendment 1 (05-Feb-2024, non-substantial, country-specific for the UK).	Administrative change.
Section 12.8 Appendix 8: Protocol amendment history	Section updated. Added Amendment 1 (05-Feb-2024, non-substantial, country-specific for the UK).	Administrative change.
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarized.

Abbreviations: please refer to the list of abbreviations.

Table of contents

List of panels

List of abbreviations

Ab	antibody
AD	atopic dermatitis
ADA	anti-drug antibodies
ADSD	Atopic Dermatitis Symptom Diary
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
anti-HCV	hepatitis C virus antibody
APC	antigen-presenting cell
AST	aspartate aminotransferase
AUC	area under the curve
BP	blood pressure
BSA	body surface area
CA	Canada
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CMO	contract manufacturing organization
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	corona virus disease 2019
CPM	clinical project manager
CRA	clinical research associate
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTIS	Clinical Trials Information System
CTR	clinical trial report
CZ	Czech Republic
DE	Germany
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid

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
EASI-100	100% reduction in EASI score
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQol 5-Dimension Health Questionnaire 5 Level
ES	Spain
EU	European Union
FAS	full analysis set
FDA	United States Food and Drug Administration
FiH	first in human
FR	France
GCP	Good Clinical Practice
GCTM	global clinical trial manager
HADS	Hospital Anxiety and Depression Scale
HbA1c	glycated haemoglobin
HBsAg	hepatitis B surface antigen
HCP	healthcare professional
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HU	Hungary
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICHS6 (R1)	Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals
ICS-LABA	inhaled corticosteroid-long-acting beta-2-agonist
ID	identification number

IEC	independent ethics committee
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-4	interleukin 4
IL-4Rα	interleukin 4 receptor α
IL-5	interleukin 5
IL-10R2	interleukin 10 receptor 2
IL-13	interleukin 13
IL-17	interleukin 17
IL-22	interleukin 22
IL-22BP	interleukin 22 binding protein
IL-22R	interleukin 22 receptor
IL-22RA1	interleukin 22 receptor subunit alpha 1
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	institutional review board
IRT	interactive response technology
IT	information technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
JAK	janus kinase
JAK1	janus kinase 1
JP	Japan
KLH	keyhole limpet hemocyanin
LEO Pharma	LEO Pharma A/S
LLQ	lower level of quantification
LSmean	least squares mean
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
MNAR	missing not at random
mRNA	messenger ribonucleic acid
NBUVB	narrow band ultraviolet B
NOAEL	no observed adverse effect level
PCR	polymerase chain reaction
PD	pharmacodynamics
PDE-4	phosphodiesterase-4
PEF	peak expiratory flow
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetics
PL	Poland
POEM	Patient-Oriented Eczema Measure
PRO	patient-reported outcome
PT	preferred term
PUVA	psoralen + ultraviolet A
qPCR	quantitative polymerase chain reaction
QW	every week
Q2W	every 2 weeks
RNA	ribonucleic acid
RO	Romania
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCORAD	SCORing Atopic Dermatitis
SD	standard deviation
SOC	system organ class
STAT3	signal transducer and activator of transcription 3
SUSAR	suspected, unexpected serious adverse reaction

TCI	topical calcineurin inhibitor(s)
TCS	topical corticosteroid(s)
TEAE	treatment-emergent adverse event
TMDD	target-mediated drug disposition
UK	United Kingdom
ULN	upper limit of normal
US	United States
UVA1	ultraviolet A1
UVB	ultraviolet B
VAS	Visual Analogue Scale
vIGA-AD	validated Investigator Global Assessment Scale for Atopic Dermatitis
WPAI-SHP	Work Productivity and Activity Impairment: Specific Health Problem

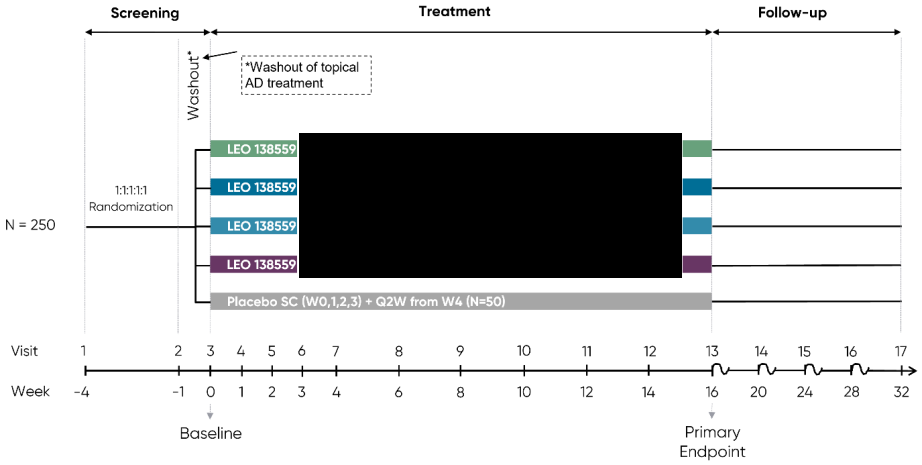
1 Protocol summary

1.1 Protocol synopsis

Trial ID	LP0145-2240
Protocol title	A phase 2b, randomized, double-blind, placebo-controlled, multi-site, parallel-group, dose-finding trial to evaluate the efficacy and safety of different doses of subcutaneously (SC) administered LEO 138559 in adult subjects with moderate-to-severe atopic dermatitis.
Brief title	A trial to evaluate the efficacy and safety of different doses of LEO 138559 in adults with moderate-to-severe atopic dermatitis.
Regulatory agency identifier numbers	Universal trial number: U1111-1286-0955 ClinicalTrials.gov ID: NCT05923099 IND number: 146054 EU CT number: 2022-500777-14 Japanese trial registration number: 2023-1450
Trial rationale	Despite the recent improvements in treatment, there still remains an unmet need for more safe and efficacious treatments to be used long-term for moderate-to-severe atopic dermatitis patients. Management of moderate-to-severe AD is challenging because of the chronicity of the disease and the limited therapeutic options that are both efficacious and have an acceptable long-term safety profile. A 'control-based' and 'risk-based' model of disease management in which an initial diagnosis is followed by treatment according to categorization of severity is usually recommended. The pharmacological treatment algorithm for AD progresses from mild topical anti-inflammatory therapy to high-potency topical anti-inflammatory therapy, and in more severe cases leads to systemic immunomodulating therapy. In general, the national treatment guidelines recommend the use of systemic treatment in patients who are refractory to optimized topical therapies. Despite promising efficacy, the dupilumab pivotal trials showed that more than 60% of the trial participants with AD did not meet the primary endpoint of Investigator's Global Assessment 0/1 (IGA 0/1) or clear/almost clear skin. Further, tralokinumab and janus kinase (JAK) inhibitors have been recently approved, but even with those advances, there remains an unmet need to develop new therapies with improved efficacy and/or safety. Further, it is increasingly recognized 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. LEO 138559 is a mAb that binds to the interleukin 22 receptor subunit alpha 1 (IL-22RA1) subunit of the IL-22 receptor, thereby blocking the binding of the ligand (IL-22). The results from the LP0145-1315, phase 1, first in human (FiH) trial indicated a clinical effect of both [redacted] mg and [redacted] mg every week (QW) for up to 5 weeks in moderate-to-severe AD subjects followed for 17 weeks. In addition, the results from the LP0145-1376, phase 2a, proof-of-concept trial showed evidence of a clinical effect seen in the LEO 138559 450 mg Q2W group versus placebo in adult subjects with moderate-to severe AD, meeting

<table>
<tr><td></td><td>the primary endpoint (improvement in Eczema Area and Severity Index [EASI] score) and with no major safety concerns identified.
In summary, based on the mode of action of LEO 138559, and the findings in the phase 1 and phase 2a trials, it is expected that LEO 138559 is a safe and efficacious treatment for patients with moderate-to-severe AD.
All doses studied so far have had an acceptable benefit/risk profile and no major safety concerns have been identified.</td></tr>
<tr><td>Ethical considerations</td><td>This trial will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki and ICH GCP and in compliance with the approved protocol and applicable regulatory requirements.
The trial design is considered scientifically justified and considered 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. There is a clear unmet need for safe, long-term treatment options for subjects with moderate-to-severe AD, and the novel IL-22RA1 antagonist, LEO 138559, is expected to be efficacious in AD treatment. 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. Risks to subjects in the trial will be minimized by inclusion of subjects fulfilling all eligibility criteria.</td></tr>
<tr><td>Main objectives, endpoints, and estimands</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 4 different dose regimens of LEO 138559 with placebo in subjects with moderate-to-severe AD.</td><td>Primary endpoint
• Percent change in EASI[1] score from baseline to Week 16.</td></tr>
<tr><td>Secondary objective</td><td>Secondary endpoint</td></tr>
<tr><td>To compare the safety of 4 different dose regimens of LEO 138559 with placebo in subjects with moderate-to-severe AD.</td><td>• Number of treatment-emergent adverse events (TEAEs) recorded for each subject from baseline to Week 16.</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>

The primary estimand for the primary endpoint attempts to quantify the effect of treatment, in the hypothetical scenario, where subjects do not permanently discontinue IMP for any reason and where rescue treatment is not made available.</td></tr>
<tr><td>Trial design</td><td>The trial design is illustrated in the figure below:</td></tr>
</table>

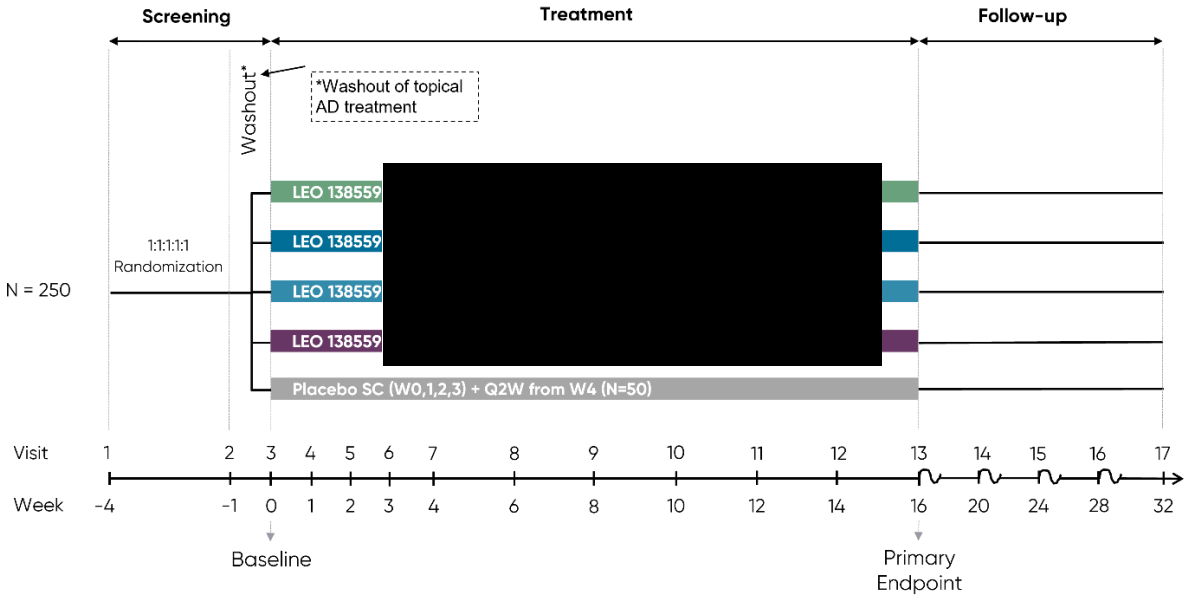
	 In addition to placebo administrations to subjects in the placebo group (at Weeks 0, 1, 2, 3, 4, 6, 8, 10, 12, 14), placebo administrations will also be used to mask the weekly loading doses and the different dose levels of active IMP. **Abbreviations:** AD = atopic dermatitis; N = number of subjects; SC = subcutaneously; Q2W = every 2 weeks; W = Week. This is a phase 2b, randomized, double-blind, placebo-controlled, multi-site, parallel-group, dose-finding trial to evaluate the efficacy and safety of different doses of SC administered LEO 138559 in adult subjects with moderate-to-severe atopic dermatitis. The trial will consist of a screening period of up to 4 weeks (including an applicable washout period of 1 week for topical AD treatment), a treatment period of 16 weeks, and a 16-week follow-up period. Assessments will include efficacy, safety, pharmacokinetics (PK), and anti-drug antibodies (ADAs) assessments. At the start of the washout period, subjects will stop any treatment with topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), topical phosphodiesterase 4 (PDE-4) inhibitors, topical JAK inhibitors, or other medicated topical treatments. Subjects should continue using their current daily skin care moisturizing routine from screening throughout the trial (until Week 32), if approved by the investigator, who will otherwise make an alternative suggestion. At Day 1 (baseline), eligible subjects will be randomized 1:1:1:1:1 to 1 of 5 dose regimens: LEO 138559 (4 different dose regimens) or placebo.
Brief summary	The purpose of this trial is to compare the efficacy, health-related quality of life, and safety of LEO 138559 with placebo administered as subcutaneous injections in adult subjects with moderate-to-severe atopic dermatitis. The treatment will be initiated with loading doses within the first 4 weeks and followed by dosing every 2 weeks for the rest of the treatment period. The treatment duration will be 16 weeks, and the trial duration will be up to 36 weeks. The visit frequency will be weekly, every 2 weeks, or every 4 weeks depending on the trial period (screening, treatment period, or follow-up).
Number of subjects	A total of approximately 250 subjects (at least 25 Japanese subjects) will be randomized 1:1:1:1:1 to 1 of 5 treatment groups: LEO 138559 (4 different dose regimens) or placebo.

Treatment groups and duration	For each subject the trial will last at least 33 weeks and up to 36 weeks, including: • A screening period of up to 4 weeks (from Week -4 up to Week 0) including an applicable washout period of 1 week for topical AD treatment (from Week -1 up to Week 0). • A treatment period of 16 weeks (from Week 0 up to Week 16) with subjects randomized into 1 of 4 active treatment groups or a placebo treatment group. • A follow-up period of 16 weeks (from Week 16 up to Week 32) for the assessment of efficacy, safety, PK, and ADAs. 4 different LEO 138559 dose regimens and 1 placebo regimen of bi-weekly SC injections, each with a preceding loading dose regimen, will be tested: • Dose regimen 1: LEO 138559 [redacted] mg SC Weeks 0, 1, 2, 3 and then [redacted] mg SC Q2W from Week 4 (50 subjects). • Dose regimen 2: LEO 138559 [redacted] mg SC Weeks 0, 1, 2 and then [redacted] mg SC Q2W from Week 4 (50 subjects). • Dose regimen 3: LEO 138559 [redacted] mg SC Weeks 0 and 2 and then [redacted] mg SC Q2W from Week 4 (50 subjects). • Dose regimen 4: LEO 138559 [redacted] mg SC Weeks 0 and 2 and then [redacted] mg SC Q2W from Week 4 (50 subjects). • Placebo regimen: Placebo SC Weeks 0, 1, 2, 3 and then placebo SC Q2W from Week 4 (50 subjects).
DMC / Other Committee	No

1.2 Schematic of trial design

The trial design is illustrated in Panel 1 and described in Section 4.1.

Panel 1: Trial design



In addition to placebo administrations to subjects in the placebo group (at Weeks 0, 1, 2, 3, 4, 6, 8, 10, 12, 14), placebo administrations will also be used to mask the weekly loading doses, and the different dose levels of active IMP.

Abbreviations: AD = atopic dermatitis; N = number of subjects; SC = subcutaneously; Q2W = every 2 weeks; W = Week.

1.3 Schedule of activities

Panel 2 presents schedule of trial activities specific for CA, JP, UK and US. For schedule of trial activities specific for EU countries i.e. CZ, DE, ES, FR, HU, PL and RO, see Section 12.5.1.1 (Panel 18).

Panel 2: Schedule of trial activities

	Screening[a]		Treatment period											Follow-up				Early term, if app.[b),c),d)]	Uns. visit[e)]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EoT[b)]**	**14**	**15**	**16**	**17[b),c)]**			
Week	**-4**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16[b)]**	**20**	**24**	**28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**			
Visit window (days)[f)]	**NA**	**-3**	**NA**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Administrative and baseline procedures																				
Informed consent[g)]	X																			App 1 (12.1.3)
Subject eligibility	X		X																	5.2 and 5.3
Demographics	X																			8.2.1
Medical history	X																			8.2.2
Body measurement (height)	X																			8.2.3
Serum pregnancy test[h)]	X																			8.2.5
C-SSRS	X																			8.2.4

	Screening[a]		Treatment period											Follow-up				Early term, if app.[b],[c],[d]	Uns. visit[e]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EoT[b]**	**14**	**15**	**16**	**17[b],[c]**			
Week	**-4**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16[b]**	**20**	**24**	**28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**			
Visit window (days)[f]	**NA**	**-3**	**NA**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Treatments and randomization																				
Randomization			X[k]																	6.3
IMP administration[o] and compliance			X	X	X	X	X	X	X	X	X	X							(X)	6.2 and 6.8.3
Background treatment (moisturizer)[i]	<==========																==========>			6.4
Concomitant medication[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	6.6
Concurrent procedures[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	6.6
Assessments of efficacy: Investigator assessments																				
EASI	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	8.3.1
SCORAD	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	8.3.2
vIGA-AD	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	8.3.3
Assessments of efficacy: Subject assessments																				
eDiary hand-out/training	X																			

	Screening[a)]		Treatment period											Follow-up				Early term, if app.[b),c),d)]	Uns. visit[e)]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EoT[b)]**	**14**	**15**	**16**	**17[b),c)]**			
Week	**-4**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16[b)]**	**20**	**24**	**28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**			
Visit window (days)[f)]	**NA**	**-3**	**NA**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Return of eDiary																	X			
eDiary completion[l)]		<==========																===>		8.3.5.1
DLQI			X	X			X		X		X	X	X					(X)	(X)	8.3.5.6
POEM			X	X			X		X		X	X	X					(X)	(X)	8.3.5.7
EQ-5D-5L			X				X		X		X	X	X					(X)	(X)	8.3.5.8
WPAI-SHP			X										X					(X)	(X)	8.3.5.9
HADS			X										X					(X)	(X)	8.3.5.10
PGI-S[m)]			X				X		X		X	X	X					(X)	(X)	8.3.5.11
PGI-C[n)]							X		X		X	X	X					(X)	(X)	8.3.5.12
Assessments of safety																				
Vital signs[o)]	X		X	X	X	X	X		X		X		X	X			X	(X)	(X)	8.4.1
Physical examination	X		X										X					(X)	(X)	8.4.2
Body measurement (weight)	X		X										X					(X)	(X)	8.4.3
ECG	X		X				X		X				X				X	(X)	(X)	8.4.4
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	10

	Screening[a)]		Treatment period											Follow-up				Early term, if app.[b),c),d)]	Uns. visit[e)]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EoT[b)]**	**14**	**15**	**16**	**17[b),c)]**			
Week	**-4**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16[b)]**	**20**	**24**	**28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**			
Visit window (days)[f)]	**NA**	**-3**	**NA**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Laboratory tests																				
Hepatitis B and C, HIV	X																			8.2.5
Tuberculosis test	X																			8.2.5
Chemistry and hematology (central laboratory)	X		X				X		X		X		X	X			X	(X)	(X)	8.4.5
IgE	X		X				X		X		X		X	X			X	(X)	(X)	8.4.5
Urinalysis (urine dipstick)	X		X				X		X		X		X	X			X	(X)	(X)	8.4.5
Urine pregnancy test			X				X		X		X		X	X	X	X	X	(X)	(X)	8.4.5
ADA			X		X								X	X			X	(X)	(X)	8.4.6
Other assessments: Pharmacokinetics																				
Blood sample (LEO 138559 serum concentration)[p)]				X	X		X		X		X		X	X			X	(X)	(X)	8.5

	Screening[a)]		Treatment period											Follow-up				Early term, if app.[b),c),d)]	Uns. visit[e)]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EoT[b)]**	**14**	**15**	**16**	**17[b),c)]**			
Week	**-4**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16[b)]**	**20**	**24**	**28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**			
Visit window (days)[f)]	**NA**	**-3**	**NA**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Other assessments: Pharmacodynamics																				
Blood sample (biomarkers)			X		X		X		X				X					(X)	(X)	8.6
Skin swabs (*Staphylococcus aureus* abundance) and microbiome profiling			X										X					(X)	(X)	8.6
Skin tape strips (molecular profile)[q)]			X				X						X					(X)	(X)	8.6
Skin biopsies (biomarker expression)[r)]			X										X							8.6

	Screening[a]		Treatment period											Follow-up				Early term, if app.[b),c),d)]	Uns. visit[e)]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EoT[b)]**	**14**	**15**	**16**	**17[b),c)]**			
Week	**-4**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16[b)]**	**20**	**24**	**28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**			
Visit window (days)[f)]	**NA**	**-3**	**NA**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Other assessments: Photography																				
Photography[s)]			X				X		X		X		X					(X)	(X)	8.7.1
Qualitative interviews in CA, UK and US[t)]																				
Scheduling interview										X										8.7.2
Clinigma to conduct trial interviews												X								8.7.2
End of treatment/trial																				
End of treatment[u)]													X					X	(X)	8.8
End of trial[v)]																	X	X[w)]	(X)	8.8

a) The screening period has a maximum duration of 4 weeks, with 2 planned visits. Visit 2 can be conducted by phone or on site.

b) Subjects who permanently discontinue IMP for any reason will be asked to attend an early termination visit as soon as possible after discontinuation of IMP. Subjects should be encouraged to attend all trial visits and be assessed for safety and efficacy according to the schedule of assessments. For subjects who no longer wish to attend all trial visits, the following visits should be prioritized: The primary endpoint visit (i.e. the Week 16 visit) and a final follow-up visit 18 weeks after last administration of IMP (with assessments identical to those to be done at the regular Week 32 visit).

c) Subjects who withdraw from the trial prior to Week 16 will be asked to attend an early termination visit as soon as possible after withdrawal (with assessments identical to those to be done at the regular Week 32 visit).

d) Some assessments to be performed at early termination visits will be at the discretion of the investigator. These are marked with an (X) in the table.

e) Assessments to be performed at unscheduled visits will be at the discretion of the investigator (marked with an (X) in the table).

f) 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 randomization/baseline.

g) The ICF must be signed prior to performing any protocol-related procedures, including, but not limited to, screening evaluations and washout of prohibited medications.

h) Only for women of childbearing potential (as defined in inclusion criterion no. 10).

i) Subjects should continue using their current daily skin care moisturizing routine from screening throughout the trial (until Week 32), if approved by the investigator, who will otherwise make an alternative suggestion.

j) Any medication, vaccine, or procedure received/performed from 3 months (12 months for medications related to AD) prior to screening through end of trial must be recorded.

k) In order to ensure a sufficient number of subjects naive for biologics and systemic JAK inhibitors used for their AD, there will be a capping at 50% of subjects who received prior treatment with such therapies. These capping criteria will also apply for Japanese subjects.

l) Nocturnal [redacted], Difficulty [redacted], and Frequency of [redacted] During the Night (to be completed in the morning), and ADSD (to be completed in the evening) will be initiated at least 7 days prior to baseline (Day 1) and will be completed in the eDiary daily. After Week 16, only ADSD will be completed. Subjects who discontinue IMP, but remain in the trial, will continue completing the eDiary until the Week 16 visit.

m) PGI-S includes: [redacted], ADSD, Nocturnal [redacted], Difficulty [redacted], and Frequency of [redacted] During the Night.

n) PGI-C includes: [redacted], ADSD, Nocturnal [redacted], Difficulty [redacted], and Frequency of [redacted] During the Night.

o) Vital signs must be assessed prior to IMP administration. In addition, at Weeks 0, 1, 2, 3, and 4, subjects will be monitored after IMP administration for potential immediate drug reactions for a minimum of 2 hours with vital signs taken immediately (within 5 minutes) after last IMP administration as well as after 30 minutes (± 5 minutes), after 1 hour (± 5 minutes), and after 2 hours (± 5 minutes), or until stable, whichever is later.

p) Samples to be collected pre-dose.

q) Skin tape strips will be collected at selected trial sites.

r) Skin biopsies will be collected at selected trial sites. It is voluntary for subjects at these sites to have skin biopsies collected, and if done, they will need to have provided informed consent to this component. Paired lesional and non-lesional biopsies will be collected at baseline. At the post-baseline visit, 1 biopsy will be collected from the original lesion; no skin biopsy will be collected from non-lesional skin at the post-baseline visit.

s) Photography will be performed at selected trial sites. It is voluntary for subjects at these sites to have photographs taken, and if done, they will need to have provided informed consent to this component.

t) Interviews will be conducted at selected trial sites. The interview will be scheduled to occur as soon as possible and within 14 days after Week 14 (Visit 12).

u) An end-of-treatment form must be completed once in the eCRF for all subjects exposed to IMP either at Week 16 or early termination.

v) An end-of-trial form must be completed in the eCRF for all subjects randomized and/or exposed to IMP.

w) Only applicable to subjects who withdraw from the trial prior to Week 16.

Abbreviations: AD = atopic dermatitis; ADA = anti-drug antibodies; ADSD = Atopic Dermatitis Symptom Diary; AE = adverse event; app = applicable; CA = Canada; C-SSRS = Columbia-Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eCRF = electronic case report form; eDiary = electronic diary; EoT = end-of-treatment; EQ-5D-5L = EuroQoL 5-Dimension Health Questionnaire 5 Level; HADS = Hospital Anxiety and Depression Scale; HIV = human immunodeficiency virus; ICF = informed consent form; IgE = immunoglobulin E; IMP = investigational medicinal product; JAK = janus kinase; NA = not applicable; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; term = termination; Uns = unscheduled; UK = United Kingdom; US = United States; vIGA-AD = validated Investigator's Global Assessment for atopic dermatitis; WPAI-SHP = Work Productivity and Activity Impairment: Specific Health Problem.

2 Introduction and trial rationale

2.1 Atopic dermatitis

AD is a chronic inflammatory skin disease characterized by recurrent widespread inflamed and dry skin lesions, intractable itch, and increased susceptibility to bacterial, viral, and fungal skin infections (2-5). 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 skin pain leading to poor quality of life, sleep deprivation, mood changes, and lost productivity (6-8). AD is the most common inflammatory skin disorder with a lifetime prevalence of 15–20% (9). 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 (2, 10).

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 APCs and recruit Th2 cells and innate lymphoid cells (11, 12). These cells amplify the type 2 immune response by secreting IL-4, IL-5, and IL-13 (13-15). As AD progresses from acute to chronic, a mixed T cell infiltrate including Th17 and Th22 cells develops (16). These cells secrete IL-17 and IL-22, which have been reported to play a role in AD pathogenesis (17, 18). Whether IL-22 is a key driver of AD pathogenesis remains unknown.

Topical therapies are the mainstay of treatment for AD and include moisturizers, TCS, TCI, and PDE-4 inhibitors (19). The topical JAK inhibitor ruxolitinib (cream) has received marketing approval in the US (20, 21), and the topical JAK inhibitor delgocitinib (ointment) has received marketing approval in Japan (22, 23). If disease control cannot be achieved with topical treatments, phototherapy can be considered (24).

For patients with moderate-to-severe AD, topical therapy and phototherapy are often insufficient or impractical, and therefore systemic therapy is indicated. Conventional systemic therapies that patients are generally started on 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. Azathioprine, methotrexate, and mycophenolate mofetil have demonstrated varying levels of efficacy (25, 26) and are used off-label. For patients who do not respond to these conventional systemic therapies or for whom these therapies are contraindicated, biologics are usually considered first line, both in Europe and the US. In 2017, the first biologic was approved for

the treatment of moderate-to-severe AD (dupilumab, anti-IL-4Rα mAb) (27-29). Tralokinumab (anti-IL-13 mAb) was approved in Europe and the US (30-32) in 2021, and was approved in Japan in 2022 (33). Also in 2022, nemolizumab was approved in Japan for the treatment of itching associated with AD (34). In addition, several targeted biologic therapies are in development for AD, including lebrikizumab and nemolizumab (35, 36). Second line therapies for patients not responding to conventional systemics or biologics, or for whom those therapies are contraindicated, are the JAK inhibitors. Several JAK inhibitors have been approved in Europe, the US, and Japan (34, 37-46). However, use of systemic JAK inhibitors has been associated with safety concerns and limited knowledge is currently available on safety with long-term use (47, 48).

2.2 Experience with IMP

2.2.1 Non-clinical data

2.2.1.1 Pharmacology

LEO 138559 binds to the IL-22RA1 with a dissociation constant of [redacted] pM (assessed by surface plasmon resonance). LEO 138559 inhibits the binding of IL-22 to its receptor with a half-maximal inhibitory concentration value of [redacted] pM measured by blockade of induction of [redacted] release, and thereby leads to full inhibition of the signaling induced by IL-22 in human primary dermal keratinocytes. An approximate 1:1 ratio between binding and inhibition is demonstrated. Importantly, LEO 138559 inhibits IL-22 induced signals in intact human skin in a reconstructed 3D skin equivalent skin model. In this skin model, LEO 138559 reverses both inflammatory markers, and normalizes skin barrier markers. Furthermore, LEO 138559 inhibits [redacted] signaling in cells harboring the IL-22RA1:IL-20R2 dimer. LEO 138559 is devoid of any agonistic potential.

Species cross reactivity was shown by similar binding of LEO 138559 to cynomolgus, rhesus monkey, and human IL-22RA1, whereas no binding to rodent, dog, or rabbit IL-22RA1, and only very weak binding to pig IL-22RA1, was observed. Furthermore, functional inhibition of cynomolgus IL-22RA1 was demonstrated in both transfected cells and intact cynomolgus skin ex vivo stimulated by IL-22. Lastly, LEO 138559 also lowered the imiquimod-induced skin inflammatory phenotype in cynomolgus monkeys.

The risk of adverse Fc effector function of LEO 138559, such as Ab-dependent cellular cytotoxicity or complement-dependent cytotoxicity, is low as it has been demonstrated that there is no or very weak binding to FcγRs and low complement fixation potential.

A detailed overview of non-clinical data on LEO 138559 is available in the current investigator's brochure (49).

2.2.1.2 PK

The non-clinical PK of LEO 138559 was assessed in cynomolgus monkeys following single and multiple IV and SC administrations.

LEO 138559 displayed typical IgG kinetics with a half-life of approximately [redacted] days and linear kinetics at higher doses but with a more than dose-proportional decrease in exposure (AUC) at lower doses due to TMDD. The absolute SC bioavailability of LEO 138559 at the 100 mg/kg/week dose level was [redacted] for males and [redacted] for females.

In all toxicology studies, except for 1 monkey in the 26-week study with high ADA titres, sufficient and sustained exposure to LEO 138559 was demonstrated at all dose levels throughout the entire dosing period with no indication of ADA formation affecting exposure or causing adverse effects.

A detailed overview of non-clinical data on LEO 138559 is available in the current investigator's brochure (49).

2.2.1.3 Toxicology

The cynomolgus monkey was chosen as the most relevant non-clinical species for evaluation of local and systemic toxicities of LEO 138559, which was shown to bind to the cynomolgus monkey IL-22R with near-equivalent potency as compared with the human IL-22R.
LEO 138559 is also pharmacodynamically active in cynomolgus monkeys, as shown by its ability to reduce imiquimod-induced skin thickness and reverse IL-22-mediated filaggrin-2 mRNA reduction.

Following multiple SC or IV doses of LEO 138559 in cynomolgus monkeys, there were no local or systemic toxicities, resulting in a NOAEL of 100 mg/kg/week, the highest dose tested (based on studies of 4- and 26-weeks of dosing duration).

The 26-week cynomolgus study used sexually mature animals and included a fertility assessment. In males, there were no effects on sperm motility, sperm morphology, or testicular spermatogenesis. In females, menstrual cycle data were not affected by administration of LEO 138559.

There were no LEO 138559-related effects on safety pharmacology endpoints evaluating the respiratory, cardiovascular, and central nervous systems in repeated-dose toxicity studies in cynomolgus monkeys at doses up to 100 mg/kg (SC and IV).

No evidence of immunotoxicity or generalized immune suppression was found in cynomolgus monkeys, with assessments including standard hematology, immunophenotyping, immune organ histopathology, and functional assessment. Due to the absence of IL-22RA1 on immune cells and lack of Ab effector function, no immunosuppression is expected upon IL-22RA1 blocking.

In a cytokine release assay, LEO 138559, either immobilized or soluble, did not stimulate the release of pro-inflammatory cytokines or chemokines at any test concentration (up to 100 µg/mL).

In conclusion, the LEO 138559 non-clinical data indicated a toxicity profile that is amenable to clinical monitoring, is of low concern for human risk, and provides an approximate [redacted]-fold margin of exposure between the NOAEL and the expected human exposure at steady state following [redacted] mg Q2W dosing.

A detailed overview of non-clinical data on LEO 138559 is available in the current investigator's brochure (49).

2.2.2 Clinical data

To date, clinical data are available from 3 completed trials (defined as trials with a final clinical trial report); a phase 1 FiH trial (LP0145-1315), a phase 1 PK and safety trial (LP0145-1486) in Japanese subjects living in the US, and a phase 2a trial (LP0145-1376).

LP0145-1315 was a phase 1, randomized, double-blind, placebo-controlled, multi-center, SAD, and MAD trial that evaluated the safety, tolerability, PK, and PD of LEO 138559 in healthy volunteers and subjects with moderate-to-severe AD. The trial consisted of 2 parts: SAD and MAD.

In the LP0145-1315 trial, single IV doses up to [redacted] mg LEO 138559 or placebo and single SC doses up to [redacted] mg LEO 138559 or placebo were administered to healthy subjects. LEO 138559 or placebo were administered SC as once weekly doses in healthy subjects ([redacted] mg) and in AD subjects ([redacted] and [redacted] mg) for 5 weeks. In total, 35 subjects were dosed with LEO 138559 in this trial. In AD subjects, a reduction in disease severity based on individual EASI scores was observed for LEO 138559 (both the [redacted] mg and [redacted] mg QW dose regimens) compared with placebo. No SAEs and no AE patterns giving rise to any concerns were reported. No risks for humans were identified at the dose levels tested.

Prior to LP0145-1315, there was no clinical experience of administering LEO 138559 to humans. However, the anti-IL-22 mAb fezakinumab (ILV-094, Pfizer) was well tolerated

when administered IV to AD subjects and improved disease scores in subjects with severe AD after 12 weeks in a phase 2a trial (50). 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 (51).

The LP0145-1486 trial was a phase 1 clinical trial conducted in 24 Japanese healthy volunteers with the aim of evaluating the PK and safety of single SC administration of LEO 138559 ([redacted] mg, [redacted] mg, or [redacted] mg) or placebo. In this trial, the PK was as expected for the population. TMDD was observed at the lowest dose level ([redacted] mg). As a result of [redacted] dependency of the PK of LEO 138559, higher serum concentration was observed in Japanese subjects as compared to non-Japanese subjects due to a lower [redacted] of Japanese subjects. However, Japanese subjects are expected to have the same exposure as non-Japanese subjects if the [redacted] is the same, and the benefit/risk profile is thus not changed for Japanese subjects.

In a phase 2a trial (LP0145-1376), adults with moderate-to-severe AD were treated with LEO 138559 or placebo. A total of 58 subjects were randomized 1:1 into the 2 treatment groups, either LEO 138559 450 mg Q2W (with an additional LEO 138559 450 mg administration at Week 1) or placebo Q2W (with an additional placebo administration at Week 1), to evaluate the safety and efficacy over a treatment period of 16 weeks, followed by a 16-week follow-up period. The primary endpoint was change from baseline in EASI score at Week 16. The secondary endpoint was the number of TEAEs from baseline to Week 16. In this phase 2a trial, the primary endpoint was met, with a statistically significant improvement in EASI score at Week 16 in the LEO 138559 450 mg Q2W group versus placebo. Fewer subjects in the LEO 138559 group (7 subjects) than in the placebo group (11 subjects) discontinued IMP and/or withdrew from the trial. The most frequent reasons for IMP discontinuation were: AEs in the LEO 138559 group (6 subjects, of which 4 had AEs related to COVID-19 infection) and withdrawal by subject in the placebo group (7 subjects). Note that as per protocol, subjects that were positive for SARS-CoV-2 (COVID-19) had to permanently discontinue IMP. No SAEs and no AE patterns giving rise to any concerns were reported.

2.2.3 PK

Based on the human PK data from the LP0145-1315, LP0145-1486 and LP0145-1376 trials, the PK of LEO 138559 is as expected for a mAb directed towards 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 [redacted] days. After multiple dosing, the elimination half-life was observed to be between [redacted] days. At and above the exposure level relevant for clinical testing (dose ≥[redacted] mg Q2W), the elimination is dominated by linear clearance and close to dose proportionality is expected at steady state. Following administration of [redacted] mg Q2W, average C_{trough} at steady state was approximately [redacted] µg/mL with a maximum observed value of [redacted] µg/mL.

A detailed overview of clinical data on LEO 138559 is available in the current investigator's brochure (49).

2.3 Trial rationale

Despite the recent improvements in treatment, there still remains an unmet need for more safe, long-term treatment options for patients with moderate to-severe AD. Management of moderate-to-severe AD is challenging because of the chronicity of the disease and the limited therapeutic options that are both efficacious and have an acceptable long-term safety profile. A 'control-based' and 'risk-based' model of disease management in which an initial diagnosis is followed by treatment according to categorization of severity is usually recommended. The pharmacological treatment algorithm for AD progresses from mild topical anti-inflammatory therapy to high-potency topical anti-inflammatory therapy, and in more severe cases leads to systemic immunomodulating therapy. In general, the national treatment guidelines recommend the use of systemic treatment in patients who are refractory to optimized topical therapies (24, 52-55).

Despite promising efficacy, the dupilumab pivotal trials showed that more than 60% of the trial participants with AD did not meet the primary endpoint of IGA 0/1 or clear/almost clear skin (56). Further, tralokinumab and JAK inhibitors have been recently approved, but even with those advances, there remains an unmet need for new therapies with improved efficacy and/or safety. Further, it is increasingly recognized 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 (57, 58).

LEO 138559 is a mAb that binds to the IL-22RA1 chain of the IL-22 receptor, thereby blocking the binding of the ligand (IL-22), dimerization of IL-22RA1 with IL-10R2, and downstream signaling via JAK1-STAT3 (59). LEO 138559 does not bind to the IL-22BP (IL-22RA2) thereby leaving its IL-22 inhibitory capacity intact (60).

The results from the LP0145-1315, phase 1, FiH trial indicated a clinical effect of both [redacted] mg and [redacted] mg QW for up to 5 weeks in moderate-to-severe AD subjects followed for 17 weeks. In addition, the results from the LP0145-1376, phase 2a, proof-of-concept trial showed evidence of a clinical effect seen in the LEO 138559 450 mg Q2W group versus placebo in adult subjects with moderate-to severe-AD, meeting the primary endpoint (improvement in EASI score) and with no major safety concerns identified.

In summary, based on the mode of action of LEO 138559, and the findings in the phase 1 and phase 2a trials, it is expected that LEO 138559 is a safe and efficacious treatment for patients with moderate-to-severe AD.

All doses studied so far have had an acceptable benefit/risk profile and no major safety concerns have been identified.

2.4 Ethical considerations

This trial will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki (61) and ICH GCP (1) and in compliance with the approved protocol and applicable regulatory requirements.

The trial design is considered scientifically justified and considered 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, with weekly visits for the first 4 weeks, followed by visits Q2W, and with regular laboratory tests, ECG, and vital signs. In addition, at Weeks 0, 1, 2, 3, and 4, subjects will be monitored for a period of 2 hours to detect potential immediate drug reactions **(for requirements specific for EU countries i.e. CZ, DE, ES, FR, HU, PL and RO, see Section 12.5.1)**.

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 will permanently discontinue IMP in the event of evidence of pregnancy.

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 be readily 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 subjects.

2.5 Benefit/risk assessment

There is a clear unmet need for safe, long-term treatment options for subjects with moderate-to-severe AD, and the novel IL-22RA1 antagonist, LEO 138559, is expected to be efficacious in AD treatment. Based on the phase 2a trial meeting the primary endpoint (i.e. LEO 138559 demonstrating a statistically significant difference compared to placebo in change in EASI score from baseline to Week 16), a significant proportion of the subjects are anticipated to benefit from participation in the LP0145-2240 trial as 4 in 5 subjects will receive active IMP.

IL-22R is expressed on epithelial cells and not on immune cells. IL-22 has been shown to be involved in the production of antimicrobial peptides in the skin, lungs, 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 non-clinical studies, LEO 138559 is considered immunomodulatory, but not immunosuppressive. Regarding the ability to mount effective Ab immune responses, an assessment of the effect of LEO 138559 on the immune response was performed in an immunotoxicological study in monkeys. The study concluded that KLH-specific Ab responses (IgG and IgM) to the first and second immunizations 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. hematological changes, organ weights, infections, and histology) were observed in 4- and 26-week non-clinical toxicology studies.

The LEO 138559 non-clinical data provides an approximately [redacted]-fold margin of exposure between the NOAEL and the expected human exposure at steady state for a dose of [redacted] mg Q2W (the highest dose regimen for LP0145-2240). The safety margin suggests that dosing with [redacted] mg Q2W in patients is safe with negligible risk of systemic toxicity. Considering that no adverse findings were observed in the 26-week cynomolgus studies, a safety margin of

[redacted] is justified and in line with ICHS6 (R1) which recommends a dose which provides an approximately 10-fold exposure multiple over the maximum exposure to be achieved in the clinic.

Across the 3 completed trials (LP0145-1315, LP0145-1486, and LP0145-1376), treatment with LEO 138559 was safe and well tolerated. No fatal events, no SAEs, no severe AEs, and no patterns of AEs considered related to LEO 138559 were observed. There was no apparent correlation between AEs and exposure.

The available aggregate non-clinical and clinical data from LEO 138559 have demonstrated that it is well tolerated, and no safety concerns have been identified.

Risks to subjects in the trial will be minimized by inclusion of subjects fulfilling all eligibility criteria (Sections 5.1 to 5.3) and by close clinical monitoring. Discontinuation and withdrawal criteria have also been defined.

The subjects will be informed that changes to their ongoing AD treatment may be required during the screening period and that their condition may worsen as a result. To minimize 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 subjects will also be informed of the possibility and probability of receiving active or placebo treatment. In this trial, approximately 80% 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.

If medically necessary (i.e. due to intolerable AD signs and/or symptoms), rescue treatment of AD may be provided to the subject at the discretion of the investigator. 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. bleeding into the surrounding tissue, infection at the site of injection, and, very rarely, inflammation of the vein, or formation of blood clots). Blood sampling will only be conducted by qualified medical personnel.

More detailed information about the known and expected benefits and risks, and reasonably expected AEs of LEO 138559 may be found in the investigator's brochure (49) and informed consent form.

In the event of a significant trial-continuity issue (e.g. caused by a pandemic), alternate strategies for subject visits, assessments, and monitoring may be implemented by LEO Pharma or the investigator, as per local health authority/ethics requirements (Appendix 7 [Section 12.7]).

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 favor of conducting this trial.

3 Trial objectives, estimands, and endpoints

Trial objectives and endpoints are presented in Panel 3.

An estimand framework is used 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 Panel 4 and in Section 11.

Panel 3: Objectives and endpoints

Objectives	Endpoints
Primary objective	
To compare the efficacy of 4 different dose regimens of LEO 138559 with placebo in subjects with moderate-to-severe AD.	*Primary endpoint* • Percent change in EASI score from baseline to Week 16. *Exploratory endpoints (efficacy)* • Achievement of EASI-50 at Week 16. • Achievement of EASI-75 at Week 16. • Achievement of EASI-90 at Week 16. • Achievement of EASI-100 at Week 16. • Change in EASI score from baseline to Week 16. • Change in SCORAD score from baseline to Week 16. • Percent change in SCORAD score from baseline to Week 16. • Achievement of vIGA-AD score of 0 (clear) or 1 (almost clear) at Week 16. • Change in BSA from baseline to Week 16. • Percent change in BSA from baseline to Week 16. *Exploratory endpoints (PROs)* • Reduction of ADSD Worst [redacted] score (weekly average) ≥4 from baseline to Week 16. • Change in DLQI (and individual domain scores) from baseline to Week 16. • Percent change in DLQI (and individual domain scores) from baseline to Week 16. • Change in POEM score (and individual item scores related to itch and sleep) from baseline to Week 16. • Percent change in POEM score from baseline to Week 16. • Change in EQ-5D-5L index score from baseline to Week 16. • Percent change in EQ-5D-5L index score from baseline to Week 16.

Objectives	Endpoints
	• Change in EQ-5D-5L VAS score from baseline to Week 16. • Percent change in EQ-5D-5L VAS score from baseline to Week 16. • Change in HADS score from baseline to Week 16. • Percent change in HADS score from baseline to Week 16. • Change in Difficulty [redacted] (weekly average) from baseline to Week 16. • Percent change in Difficulty [redacted] (weekly average) from baseline to Week 16. • Change in Nocturnal [redacted] (weekly average) from baseline to Week 16. • Percent change in Nocturnal [redacted] (weekly average) from baseline to Week 16. • Change in Frequency of [redacted] During the Night (weekly average) from baseline to Week 16. • Percent change in Frequency of [redacted] During the Night (weekly average) from baseline to Week 16. • Change in WPAI-SHP domain scores from baseline to Week 16. • Percent change in WPAI-SHP domain scores from baseline to Week 16. • Change in SCORAD Part C (Pruritus VAS) score from baseline to Week 16. • Percent change in SCORAD Part C (Pruritus VAS) score from baseline to Week 16.
Secondary objective	
To compare the safety of 4 different dose regimens of LEO 138559 with placebo in subjects with moderate-to-severe AD.	*Secondary endpoint* • Number of TEAEs recorded for each subject from baseline to Week 16. *Exploratory endpoint (safety)* • Time from baseline to use of any rescue treatment. • Number of TEAEs recorded for each subject from baseline to Week 32. • Number of TEAEs recorded for each subject from Week 16 to Week 32. • Having a positive ADA response from baseline to Week 32.
Exploratory objectives	
To compare the efficacy of 4 different dose regimens of LEO 138559 with	*Exploratory endpoint (PRO)*

Objectives	Endpoints
placebo in subjects with moderate-to-severe AD, having a weekly average ADSD Worst [redacted] score of ≥4 at baseline.	• Reduction of ADSD Worst [redacted] score (weekly average) ≥4 from baseline to Week 16.
To compare the efficacy of 4 different dose regimens of LEO 138559 with placebo in subjects with moderate-to-severe AD, having a DLQI score of ≥4 at baseline.	*Exploratory endpoint (PRO)* • Reduction of DLQI ≥4 from baseline to Week 16.
To compare the efficacy of 4 different dose regimens of LEO 138559 with placebo in subjects with moderate-to-severe AD, having a POEM score of ≥4 at baseline.	*Exploratory endpoint (PRO)* • Reduction of POEM ≥4 from baseline to Week 16.
To evaluate the PK of LEO 138559 in subjects with moderate-to-severe AD.	*Exploratory endpoint (PK)* • Serum concentration of LEO 138559 at Weeks 1, 2, 4, 8, 12, 16, 20, and 32.
To evaluate the effect of treatment with LEO 138559 compared with placebo for 16 weeks on biomarkers in subjects with moderate-to-severe AD.	*Exploratory endpoints (PD)* • Change in expression of biomarkers in serum from baseline to Week 2, Week 4, and to Week 16, respectively. • Change in skin *Staphylococcus aureus* abundance and microbiome profile from baseline to Week 16. • Change in skin lipid and molecular profile from baseline to Week 4, and to Week 16, respectively. • Change in biomarker expression from baseline to Week 16 in lesional skin biopsies.

Abbreviations: AD = atopic dermatitis; ADA = anti-drug antibodies; ADSD = Atopic Dermatitis Symptom Diary; BSA = body surface area; DLQI = Dermatology Life Quality Index; 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; EASI-100 = 100% reduction in EASI score; EQ-5D-5L = EuroQoL 5 Dimension Health Questionnaire 5 Level; HADS = Hospital Anxiety and Depression Scale; PK = pharmacokinetics, PD = pharmacodynamics; POEM = Patient-Oriented Eczema Measure; PRO = patient reported outcome; SCORAD = SCORing Atopic Dermatitis; TEAEs = treatment-emergent adverse events; VAS = Visual Analogue Scale; vIGA-AD = validated Investigator Global Assessment Scale for Atopic Dermatitis; WPAI-SHP = Work Productivity and Activity Impairment: Specific Health Problem.

Panel 4: Objectives, estimands, and endpoints

Objectives	Estimands				Endpoints
	Estimand type	**Strategy/ Intercurrent events**	**Target population**	**Population level summary**	
To compare the efficacy of 4 different dose regimens of LEO 138559 with placebo in subjects with moderate-to-severe AD.	Primary estimand for continuous endpoints	**Hypothetical:** - Permanent discontinuation of IMP. - Initiation of rescue treatment.	Subjects with moderate-to-severe AD.	Difference in means of the response variable between the treatment conditions.	**Primary endpoint:** • Percent change in EASI score from baseline to Week 16. **Exploratory endpoints:** • Change in EASI score from baseline to Week 16. • Change in SCORAD score from baseline to Week 16. • Percent change in SCORAD score from baseline to Week 16. • Change in BSA from baseline to Week 16. • Percent change in BSA from baseline to Week 16. • Change in DLQI (and individual domain scores) from baseline to Week 16. • Percent change in DLQI (and individual domain scores) from baseline to Week 16. • Change in POEM score (and individual item scores related to itch and sleep) from baseline to Week 16. • Percent change in POEM score from baseline to Week 16. • Change in EQ-5D-5L index score from baseline to Week 16. • Percent change in EQ-5D-5L index score from baseline to Week 16. • Change in EQ-5D-5L VAS score from baseline to Week 16.

Objectives	Estimands				Endpoints
	Estimand type	Strategy/ Intercurrent events	Target population	Population level summary	
					• Percent change in EQ-5D-5L VAS score from baseline to Week 16. • Change in HADS score from baseline to Week 16. • Percent change in HADS score from baseline to Week 16. • Change in Difficulty [redacted] (weekly average) from baseline to Week 16. • Percent change in Difficulty [redacted] (weekly average) from baseline to Week 16. • Change in Nocturnal [redacted] (weekly average) from baseline to Week 16. • Percent change in Nocturnal [redacted] (weekly average) from baseline to Week 16. • Change in Frequency of [redacted] During the Night (weekly average) from baseline to Week 16. • Percent change in Frequency of [redacted] During the Night (weekly average) from baseline to Week 16. • Change in WPAI-SHP domain from baseline to Week 16. • Percent change in WPAI-SHP domain from baseline to Week 16. • Change in SCORAD Part C (Pruritus VAS) score from baseline to Week 16. • Percent change in SCORAD Part C (Pruritus VAS) score from baseline to Week 16.

Objectives	Estimands				Endpoints
	Estimand type	**Strategy/ Intercurrent events**	**Target population**	**Population level summary**	
	Suppl. estimands for continuous endpoints	**Hypothetical supplementary:** - Permanent discontinuation of IMP. - Initiation of rescue treatment.			**Primary endpoint:** • Percent change in EASI score from baseline to Week 16. **Exploratory endpoints:** • Change in EASI score from baseline to Week 16. • Change in SCORAD score from baseline to Week 16. • Percent change in SCORAD score from baseline to Week 16. • Change in BSA from baseline to Week 16. • Percent change in BSA from baseline to Week 16. • Change in DLQI (and individual domain scores) from baseline to Week 16. • Percent change in DLQI (and individual domain scores) from baseline to Week 16. • Change in POEM score (and individual item scores related to itch and sleep) from baseline to Week 16. • Percent change in POEM score from baseline to Week 16. • Change in EQ-5D-5L index score from baseline to Week 16. • Percent change in EQ-5D-5L index score from baseline to Week 16. • Change in EQ-5D-5L VAS score from baseline to Week 16. • Percent change in EQ-5D-5L VAS score from baseline to Week 16.

Objectives	Estimands				Endpoints
	Estimand type	Strategy/ Intercurrent events	Target population	Population level summary	
					• Change in HADS score from baseline to Week 16. • Percent change in HADS score from baseline to Week 16. • Change in Difficulty [redacted] (weekly average) from baseline to Week 16. • Percent change in Difficulty [redacted] (weekly average) from baseline to Week 16. • Change in Nocturnal [redacted] (weekly average) from baseline to Week 16. • Percent change in Nocturnal [redacted] (weekly average) from baseline to Week 16. • Change in Frequency of [redacted] During the Night (weekly average) from baseline to Week 16. • Percent change in Frequency of [redacted] During the Night (weekly average) from baseline to Week 16. • Change in WPAI-SHP domain from baseline to Week 16. • Percent change in WPAI-SHP domain from baseline to Week 16. • Change in SCORAD Part C (Pruritus VAS) score from baseline to Week 16. • Percent change in SCORAD Part C (Pruritus VAS) score from baseline to Week 16.
		Treatment policy: - Permanent discontinuation of IMP.			**Primary endpoint:** Percent change in EASI score from baseline to Week 16.

Objectives	Estimands				Endpoints
	Estimand type	**Strategy/ Intercurrent events**	**Target population**	**Population level summary**	
		- Initiation of rescue treatment.			
	Primary estimand for binary endpoints	**Composite:** - Permanent discontinuation of IMP due to lack of efficacy or an AE related to worsening of AD. - Initiation of rescue treatment. **Hypothetical:** - Permanent discontinuation of IMP due to reasons other than lack of efficacy or an AE related to worsening of AD.	Subjects with moderate-to-severe AD.	Difference in response rates of the response variable between the treatment conditions.	**Exploratory endpoints:** • Achievement of EASI-50 at Week 16. • Achievement of EASI-75 at Week 16. • Achievement of EASI-90 at Week 16. • Achievement of EASI-100 at Week 16. • Achievement vIGA-AD score of 0 (clear) or 1 (almost clear) at Week 16. • Reduction of ADSD Worst [redacted] score (weekly average) ≥4 from baseline to Week 16.
			Subjects with moderate-to-severe AD, having an average ADSD Worst [redacted] score of ≥4 at baseline.		**Exploratory endpoint:** • Reduction of ADSD Worst [redacted] score (weekly average) ≥4 from baseline to Week 16.
			Subjects with moderate-to-severe AD, having a DLQI score of ≥4 at baseline.		**Exploratory endpoint:** • Reduction of DLQI ≥4 from baseline to Week 16.
			Subjects with moderate-to-severe AD, having a POEM		**Exploratory endpoint:** • Reduction of POEM ≥4 from baseline to Week 16.

Objectives	Estimands				Endpoints
	Estimand type	**Strategy/ Intercurrent events**	**Target population**	**Population level summary**	
			score of ≥4 at baseline.		
	Suppl. estimand for binary endpoints	**Treatment-policy:** - Permanent discontinuation of IMP. - Initiation of rescue treatment.	Subjects with moderate-to-severe AD.		**Exploratory endpoints:** • Achievement of EASI-50 at Week 16. • Achievement of EASI-75 at to Week 16. • Achievement of EASI-90 at Week 16. • Achievement of EASI-100 at Week 16. • Achievement vIGA-AD score of 0 (clear) or 1 (almost clear) at Week 16. • Reduction of ADSD Worst [redacted] score (weekly average) ≥4 from baseline to Week 16.
To compare the safety of 4 different dose regimens of LEO 138559 with placebo in subjects with moderate-to-severe AD.	Primary estimand for time-to-event endpoints	**While on treatment:** - Permanent discontinuation of IMP.	Subjects with moderate-to-severe AD.	Difference in the cumulative incidence at Week 16.	**Exploratory endpoint:** • Time from baseline to use of any rescue treatment.
	Suppl. estimand for time-to-event endpoints	**Composite:** - Permanent discontinuation of IMP.	Subjects with moderate-to-severe AD.	Difference in the cumulative incidence at Week 16.	**Exploratory endpoint:** • Time from baseline to use of any rescue treatment.

Abbreviations: AD = atopic dermatitis; AE = adverse events; ADSD = Atopic Dermatitis Symptom Diary; 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; EASI-100 = at least 100% decrease in EASI score; EQ-5D-5L = EuroQoL 5 Dimension Health Questionnaire 5 Level; HADS = Hospital Anxiety and Depression Scale; IMP = investigational medicinal product; POEM = Patient-Oriented Eczema Measure; Suppl. = supplementary; VAS = Visual Analogue Scale; vIGA-AD = Validated Investigator Global Assessment Scale for Atopic Dermatitis; WPAI-SHP = Work Productivity and Activity Impairment: Specific Health Problem.

4 Trial design

4.1 Overall trial design

Overview

This is a phase 2b, randomized, double-blind, placebo-controlled, multi-site, parallel-group, dose-finding 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.

For each subject the trial will last at least 33 weeks and up to 36 weeks, including:

- A screening period of up to 4 weeks (from Week -4 up to Week 0) including an applicable washout period of 1 week for topical AD treatment (from Week -1 up to Week 0).
- A treatment period of 16 weeks (from Week 0 up to Week 16) with subjects randomized into 1 of 4 active treatment groups or a placebo treatment group.
- A follow-up period of 16 weeks (from Week 16 up to Week 32) for the assessment of efficacy, safety, PK, and ADAs.

Randomization will take place at Week 0 (Day 1, baseline). 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 1.3. The trial rationale is presented in Section 2.3 and the scientific rationale for trial design is presented in Section 9.1.

Screening period (between 0 and 4 weeks prior to the baseline visit [Day 1])

Eligibility of the subject (Sections 5.1 to 5.3) to participate in the trial will be evaluated at a screening visit (Visit 1) and at the baseline visit (Visit 3). The screening visit will be performed up to 4 weeks before the baseline visit (Visit 3).

Moreover, at the screening visit (Visit 1), the subjects will receive training in completion of an eDiary and will be given an electronic device to record the ADSD, Nocturnal [redacted], Difficulty [redacted], and Frequency of [redacted] During the Night. Completion of the eDiary twice daily will be initiated at the latest 1 week prior to the baseline visit (Visit 3, Week 0).

At the start of the washout period (from Visit 2, Week -1), subjects should stop any treatment with TCS, TCI, topical PDE-4 inhibitors, topical JAK inhibitors, or other medicated topical treatments.

Subjects should continue using their current daily skin care moisturizing routine from screening throughout the trial (until Week 32), if approved by the investigator, who will otherwise make an alternative suggestion.

Randomization (Week 0)
At baseline (Visit 3, Week 0), eligibility of the subjects (Sections 5.1 to 5.3) to participate in the trial must be confirmed. Eligible subjects will be randomized 1:1:1:1:1 to 1 of 5 treatment groups: LEO 138559 (4 different dose regimens) or placebo. Randomization will be based on a permuted block design, stratified by baseline disease severity (baseline vIGA-AD score), region (Japan, Other countries), prior use of biologics or systemic JAK inhibitors for AD (Yes/No), and baseline biopsy status (willingness to provide biopsies: Yes/No). IRT will be used to control randomization and stratification factors.

Treatment period (from Week 0 up to Week 16)
In the treatment period, LEO 138559 and/or placebo injections will be administered at the site by unblinded site staff for 16 weeks, according to the treatment regimens outlined in Section 6.2.

During the treatment period, the subjects will be asked to continue applying their moisturizer, and to complete their eDiary twice daily. The subjects will also be asked to visit the clinic for assessments and procedures. Final dosing will be administered at Week 14. If medically necessary (i.e. due to intolerable AD signs and/or symptoms), rescue treatment for AD may be used from Week 4 at the discretion of the investigator (any rescue treatment, regardless of type or class, used before Week 4 will lead to permanent discontinuation of IMP) (for details, see Sections 6.5 and 7.2).

Follow-up period (from Week 16 up to Week 32)
The subject will have 4 follow-up visits at Weeks 20, 24, 28, and 32 for assessment of efficacy, safety, PK, and ADAs. Rescue treatment may be prescribed during the follow-up period at the discretion of the investigator, if medically necessary (i.e. due to intolerable AD signs and/or symptoms) (for details, see Section 6.7). In such case, subjects will continue the schedule of trial visits and assessments.

4.2 Number of subjects needed

Based on an anticipated screening failure rate of 35%, 385 subjects need to be screened for this trial to randomize approximately 250 subjects to treatment.

In order to ensure a sufficient number of subjects naive for biologics and systemic JAK inhibitors used for their AD, there will be a capping at 50% of subjects who received prior treatment with such therapies. These capping criteria will also apply for Japanese subjects.

At Week 0 (baseline), a total of approximately 250 subjects (at least 25 Japanese subjects) will be randomized to 1 of the 5 treatment regimens outlined in Section 6.2.

The statistical power considerations for this sample size are described in Section 11.1.

The trial will be conducted at approximately 90 sites in Europe, North America, and Japan.

4.3 End-of-trial definition

A subject is considered to have completed the trial if they have completed all periods of the trial including the final safety follow-up visit, regardless of early IMP discontinuation (see Section 8.8 for data to be recorded on the end-of-trial form).

The end of the trial is defined as the date of the last 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.

5 Trial population

5.1 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 1.3. 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.

5.2 Inclusion criteria

For the list of eligibility criteria specific for EU countries i.e. CZ, DE, ES, FR, HU, PL and RO, see Section 12.5.1.2. For requirements specific for JP, see Section 12.5.4.

Subjects are eligible to be included in the trial only if all of the following criteria apply:

Informed consent

1. Signed and dated informed consent as described in Appendix 1 (Section 12.1.3) has been obtained prior to any protocol-related procedures.

Age

2. 18–75 years old (both included) at screening (Visit 1). **For requirements specific for JP, see Section 12.5.4.**

Compliance

3. Willingness to comply with the clinical trial protocol.

Type of subject and disease characteristics

4. At screening, diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD ((62) and Appendix 3 [Section 12.3]).
   - History of AD for ≥1 year.
5. Subjects who have a recent history (within 12 months before screening) with documented inadequate response to treatment with TCS (±TCI as appropriate) or for whom these topical AD treatments are medically inadvisable (e.g. due to important side effects or safety risks*).

- Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to higher potency (EU class II-IV, JP ≥ Medium, US class I-V) (±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 1 year are considered as inadequate responders to TCS 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.

6. EASI score ≥12 at screening and ≥16 at baseline.
7. vIGA-AD score ≥3 at screening and baseline.
8. BSA of AD involvement ≥10% at screening and baseline.
9. ADSD Worst [redacted] score (weekly average) ≥4 at baseline. The baseline weekly average will be calculated from daily assessments of [redacted] severity during the 7 days immediately preceding the baseline visit (Day -7 to Day -1). A minimum of 4 [redacted] scores out of the 7 days is required to calculate the baseline average score.

Contraceptive/barrier requirements

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

    * A woman of childbearing potential is defined as a female subject aged ≥12 years *or* a younger girl who, at the discretion of the investigator, is deemed to be of reproductive potential. A woman is defined as not being of childbearing potential if she is postmenopausal (at least 12 months with no menses prior to screening without an alternative medical cause), 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, IUD, 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 vasectomized partner (given that the subject is monogamous).
    For requirements specific for JP, see Section 12.5.4.

5.3 Exclusion criteria

For the list of eligibility criteria specific for EU countries i.e. CZ, DE, ES, FR, HU, PL and RO, see Section 12.5.1.2. For requirements specific for JP, see Section 12.5.4.

Subjects are excluded from the trial if any of the following criteria apply:

Medical conditions

1. Major* surgery within 8 weeks prior to screening, or planned inpatient surgery or hospitalization during the trial period (*at the discretion of the investigator).
2. Active dermatologic condition that could confound the diagnosis of AD or interfere with assessment of the treatment (e.g. scabies, contact dermatitis, rosacea, urticaria, or psoriasis).
3. History of cancer, with the following exceptions:
   - Subjects who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to screening.
   - Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to screening.
4. History of or current immunodeficiency syndrome.
5. History of anaphylaxis following any biologic therapy.
6. History of clinically significant infection within 4 weeks prior to baseline which, in the opinion of the investigator, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial. Clinically significant infections are defined as:
   - a systemic infection.
   - a serious skin infection requiring parenteral (IV or intramuscular) antibiotics, antiviral, or antifungal medication.

   NOTE: Subject may be rescreened (once) after infection resolves. However, rescreening will require approval by the sponsor's medical expert (see Section 5.4).
7. Non-serious skin infection within 7 days prior to baseline. *NOTE: Subject may be rescreened (once) after infection resolves. However, rescreening will require approval by the sponsor's medical expert (see Section 5.4).*
8. Positive HBsAg or positive anti-HCV AND positive HCV-RNA at screening.
   - Subjects with a negative HBsAg and a positive anti-HBc or anti-HBs at screening will have reflex testing for HBV-DNA. Subjects who have HBV-DNA above LLQ will be excluded. **For requirements specific for EU countries i.e. CZ, DE, ES, FR, HU, PL and RO, see Section 12.5.1.2. For requirements specific for JP, see Section 12.5.4.**
9. History of HIV infection or positive HIV serology at screening.
10. Evidence of active or latent tuberculosis according to local standard of care for patients requiring initiation of a biologic treatment.
    - A tuberculosis test can be performed at the central or local laboratory. Subjects with a positive or indeterminate test at screening will be excluded. *NOTE: Subject may be retested (once) if the initial test was indeterminate.*
11. ALT or AST level ≥2.0 times the ULN at screening.

12. Uncontrolled/untreated clinically significant depression or history of attempted suicide or is at significant risk of suicide (either in the opinion of the investigator or defined as a "yes" to suicidal ideation questions no. 4 or 5 or answering "yes" to suicidal behavior on the C-SSRS Screening version).
13. Known or suspected hypersensitivity to any component(s) of the IMP.
14. Any disorder* at screening and/or baseline, which is not stable in the opinion of the investigator, and could:
    - Affect the safety of the subject throughout the trial.
    - Influence the results of the trial.
    - Impede the subject's ability to complete the trial.

    [redacted]. **For requirements specific for EU countries i.e. CZ, DE, ES, FR, HU, PL and RO, see Section 12.5.1.2.**
15. Any significant abnormal finding* at screening and/or baseline which may in the opinion of the investigator:
    - Put the subject at risk because of their participation in the trial.
    - Influence the results of the trial.
    - Influence the subject's ability to complete the trial.

    *The abnormal finding must be clinically significant and observed during the screening period. Examples include abnormal findings in physical examination, vital signs, ECG, hematology, biochemistry, or urinalysis. **For requirements specific for EU countries i.e. CZ, DE, ES, FR, HU, PL and RO, see Section 12.5.1.2.**
16. Current or recent chronic alcohol or drug abuse, or any other condition associated with poor compliance as judged by the investigator.
17. Women who are pregnant or breastfeeding.

Prior/concomitant therapy

18. Previous treatment with LEO 138559.
19. Previous exposure to fezakinumab (anti-IL-22 Ab).
20. Systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporine, azathioprine), immunomodulating drugs, retinoids (e.g. alitretinoin), corticosteroids (steroid eyedrops and inhaled or intranasal steroids are allowed), or JAK inhibitors within 28 days or 5 half-lives prior to baseline, whichever is longer.
21. Use of tanning beds or phototherapy (NBUVB, UVB, UVA1, PUVA), within 4 weeks prior to baseline.
22. Receipt of blood products within 28 days prior to screening.
23. Treatment with:
    - Any marketed or investigational biologic agents within 3 months or 5 half-lives, whichever is longer, prior to baseline.

- Any cell-depleting agents including but not limited to rituximab: within 6 months prior to baseline, or until lymphocyte count returns to normal, whichever is longer.

24. Treatment with TCS, TCI, topical PDE-4 inhibitors, topical JAK inhibitors, or other medicated topical treatments within 7 days prior to baseline. *NOTE: Subject may be rescreened (once) if failed for this criterion. However, rescreening will require approval by the sponsor's medical expert (see Section 5.4).*
25. Receipt of live attenuated vaccines 30 days prior to baseline or longer if recommended so by local guidelines.
26. 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 randomization, whichever is longer.

Prior/concurrent clinical trial experience

27. Current participation in any other interventional clinical trial.
28. Previously randomized in this clinical trial.

Other exclusion criteria

29. 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.
30. Subjects who are legally institutionalized. **For requirements specific for EU countries i.e. CZ, DE, ES, FR, HU, PL and RO, see Section 12.5.1.2.**

5.4 Screening and subjects excluded prior to randomization

Subject ID

Trial participation begins once written informed consent is obtained. Refer to Appendix 1 (Section 12.1.3) for details on the informed consent process. Once informed consent is obtained, a subject ID will be assigned by a central IRT system, and hereafter the assessment of subject eligibility may begin. The date of first screening activity could be on the same day the informed consent has been obtained, or at a later date. 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 provided written informed consent or not (screening log). This log will be anonymous and will include the reason(s) for not entering the trial, if applicable, or the allocated subject ID. 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 log must not be copied or retained by LEO Pharma.

Subjects excluded prior to randomization

Subjects excluded prior to randomization include screen failures and other subjects not subsequently assigned to trial treatment for other reasons. Screening failures are defined as subjects who consent to participate in the trial but do not meet 1 or more eligibility criteria required for participation in the trial. Other subjects not assigned to trial treatment are defined as subjects who meet the eligibility criteria but do not participate in the trial for other reasons such as lost to follow-up, withdrawal by subject, and other reasons.

To meet the CONSORT publishing requirements (63) and to respond to queries from regulatory authorities, a minimal set of information is required to ensure transparent reporting of screen failures and other subjects not assigned to trial treatment. For these subjects, the following data will be collected in the eCRF:

- Date of informed consent.
- A specification of which eligibility criteria were not met, if any.
- Date of birth (day, month, and year; only month and year; or only year, as per local legislation), age, sex, ethnicity, race **(for requirements specific for FR, see Section 12.5.3)**.
- Date of exclusion.
- Reason for exclusion.
  - Screen failure.
  - Lost to follow-up.
  - Withdrawal by subject.
  - Other (if other, a specification should be provided).
- Any AEs and SAEs.

In case of any SAEs, these must be followed up as described in Section 10.

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 for administrative or logistical reasons (e.g. delayed results or temporary site closure due to force majeure) eligibility cannot be assessed, rescreening may be permitted once. In addition, rescreening may be permitted (once) after initially having violated the exclusion criteria 6, 7, and 24. Rescreening will require approval by the sponsor's medical expert after thorough review of eCRF data from the first screening visit. Subjects to be rescreened must sign a new ICF, and all screening assessments will be re-performed. Rescreened subjects will get a new subject ID. In addition, the subject ID from the previous screening will be recorded in the eCRF.

6 Treatments

6.1 Trial product description

The IMPs included in this trial are listed in Panel 5.

Panel 5: Identification of IMPs

Investigational medicinal product	Dosage form	Active ingredient and concentration	Pack size	Manufacturer responsible for batch release
LEO 138559	Solution for injection.	LEO 138559, [redacted] mg/mL.	Vial containing 1.0 mL solution.	LEO Pharma
Placebo	Solution for injection.	Not applicable.	Vial containing 1.0 mL solution.	LEO Pharma

Note: To ensure that 1.0 mL can be withdrawn by a syringe, there will be a small overfill in the vials.
Abbreviations: IMP = investigational medicinal product.

6.2 Administration of IMP

General

Dosing visits are shown in the schedule of trial activities (Section 1.3). Dispensing of the IMP will be handled by an IRT system. The IRT system will assign the required kit numbers for each subject at each dispensing visit.

From randomization, LEO 138559 and placebo will be administered SC for a period of 14 weeks (Visits 3-12, with the last IMP administration at Week 14 [Visit 12]) according to 1 of the following treatment regimens:

- Dose regimen 1: LEO 138559 [redacted] mg SC Weeks 0, 1, 2, 3 and then [redacted] mg SC Q2W from Week 4 (50 subjects).
- Dose regimen 2: LEO 138559 [redacted] mg SC Weeks 0, 1, 2 and then [redacted] mg SC Q2W from Week 4 * (50 subjects).
- Dose regimen 3: LEO 138559 [redacted] mg SC Weeks 0 and 2 and then [redacted] mg SC Q2W from Week 4 * (50 subjects).
- Dose regimen 4: LEO 138559 [redacted] mg SC Weeks 0 and 2 and then [redacted] mg SC Q2W from Week 4 * (50 subjects).
- Placebo regimen: Placebo SC Weeks 0, 1, 2, 3 and then placebo SC Q2W from Week 4 * (50 subjects).

* In addition to placebo administrations to subjects in the placebo group (at Weeks 0, 1, 2, 3, 4, 6, 8, 10, 12, 14), placebo administrations will also be used to mask the weekly loading doses, and the different dose levels of active IMP.

The first day of dosing is considered Day 1 (Week 0). Each subject will receive a total of 3 SC injections (2 mL + 2 mL + 1 mL) per dose with either LEO 138559 or placebo, or a combination, to maintain the blinding, and to achieve a total volume of 5 mL per dose as shown in Panel 6.

Panel 6: Combinations of IMP administration per dose regimen

	LEO 138559, [redacted] mg/mL	**Placebo**
Dose regimen 1		
LEO 138559 [redacted] mg	2 x 2 mL	1 x 1 mL
Dose regimen 2		
LEO 138559 [redacted] mg	1 x 2 mL 1 x 1 mL	1 x 2 mL
Dose regimen 3		
LEO 138559 [redacted] mg (loading dose)	2 x 2 mL	1 x 1 mL
LEO 138559 [redacted] mg	1 x 2 mL	1 x 2 mL 1 x 1 mL
Dose regimen 4		
LEO 138559 [redacted] mg (loading dose)	1 x 2 mL	1 x 2 mL 1 x 1 mL
LEO 138559 [redacted] mg	1 x 1 mL	2 x 2 mL
Placebo regimen		
Placebo	-	2 x 2 mL 1 x 1 mL

Note: Placebo administrations to mask the weekly loading doses will be identical to the administrations in the placebo regimen.

During the treatment period, final dosing will be administered at Week 14 and only clinical assessment will occur at Week 16. IMP administration will continue until Week 14.

IMP will be administered by qualified, unblinded site staff as the active drug is visually distinct from placebo (see Section 6.3.2 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. It is advised that the site of injection of IMP is rotated such that the subject receives IMP at a different anatomical part (i.e. anterior thigh, abdomen or upper arm) at each treatment visit. The anatomical location of the injection (left/right anterior thigh, left/right abdominal region, left/right upper arm) must be recorded in the source documents at each treatment visit and recorded in the eCRF.

At each treatment visit, the 3 injections of IMP must be administered within a maximum of 10 minutes. The 3 injections of IMP should be administered in the same injection site area (e.g. left upper arm) separated by at least 3 cm.

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 in the trial product handling manual. IMP administration must be carried out according to these instructions.

After IMP administration

At Weeks 0, 1, 2, 3, and 4, subjects will be monitored for potential immediate drug reactions for a minimum of 2 hours after IMP administration. Vital signs will be taken immediately (within 5 minutes) after last IMP administration, as well as after 30 minutes (± 5 minutes), after 1 hour (± 5 minutes), and after 2 hours (± 5 minutes), or until stable, whichever is later **(for requirements specific for EU countries i.e. CZ, DE, ES, FR, HU, PL and RO, see Section 12.5.1)**. Vital signs will be documented in the eCRF.

As with any Ab, allergic reactions to dose administration are possible. The World Allergy Organization has categorized anaphylaxis into 2 subgroups: allergic anaphylaxis (mediated by an immunologic mechanism) and nonallergic anaphylaxis (which has a nonimmunologic cause) (64). The clinical criteria for defining anaphylaxis for this trial are listed in Appendix 4 (Section 12.4) and (65). 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 recognize and respond to anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample will be drawn from the subject 1) as soon as possible after the event, 2) at 60 minutes (± 30 minutes) after the event, and 3) 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.

- The subject is febrile (defined as ≥38°C; ≥100.4°F) within 72 hours prior to IMP administration.

From baseline to Week 4, if the trial visit cannot be rescheduled in order to maintain a minimum of 5 days to subsequent dose, the sponsor's medical expert should be contacted. From Week 4 and onwards, if the trial visit cannot be rescheduled in order to maintain a minimum of 7 days to subsequent dose, the sponsor's medical expert should be contacted.

Overdose is specified in Section 10.7.2. 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.

6.3 Treatment assignment and blinding

6.3.1 Treatment assignment

Subjects who meet all the eligibility criteria (Sections 5.1 to 5.3) will be randomized at baseline (Day 1) to receive treatment according to 1 of the treatment regimens outlined in Section 6.2.

Treatment assignment will be pre-planned according to a computer-generated randomization schedule in a 1:1:1:1:1 ratio (4 LEO 138559 dose regimens and 1 placebo regimen), based on a permuted block design and stratified by baseline disease severity (baseline vIGA-AD score), region (Japan, Other countries), prior use of biologics or systemic JAK inhibitors for AD (Yes/No), and baseline biopsy status (willingness to provide biopsies: Yes/No).

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

6.3.2 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 LEO team members, such as the unblinded CRA, unblinded GCTM, or unblinded CPM, etc.) 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 qualified, unblinded site staff 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, other trial staff involved in the management of trial subjects, or a trial subject, 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 site staff 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.

6.3.3 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 authorized LEO Pharma personnel.

Provisions are in place for 24-hour emergency unblinding of individual subject treatment. If emergency unblinding is required, the investigator can unblind a subject's treatment via the IRT system, or unblinding CRO. Only the investigator should be unblinded and keep treatment allocation confidential. LEO Pharma must remain blinded until the end of the trial.

For a requester who is not a member of the trial staff and who does not have access to the IRT system (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 1 [Section 12.1.3]) 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 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.

6.4 Background treatment

All subjects should continue using their current daily skin care moisturizing routine from screening throughout the trial (until Week 32), if approved by the investigator, who will otherwise make an alternative suggestion.

6.5 Rescue treatment

Rescue treatment is defined as the use of any of the prohibited medications or procedures listed in no. 1-6 of Section 6.7 initiated to treat intolerable AD signs and/or symptoms during the treatment and follow-up period. Rescue treatment for AD may be prescribed to trial subjects at the discretion of the investigator.

- In case rescue treatment is initiated before Week 4;
  - IMP will be permanently discontinued (see Section 7.2.1).
- In case rescue treatment is initiated at or after Week 4:
  - Subjects should preferably be started on topical treatment (TCS and/or TCI), and these subjects will continue IMP and the schedule of trial visits and assessments. Rescue treatment should only be used in situations where the subject is at risk of discontinuation, and should be continued for as short a period as possible.

    Note: It is recommended that the investigator starts with a TCI or least potent TCS for the face (e.g. hydrocortisone 1%, 2.5% cream/ointment) and moderately potent TCS for the body (e.g. triamcinolone acetonide 0.1% cream/ointment).
  - If the subject experiences intolerable AD signs and/or symptoms and the TCS and/or TCI rescue treatment is insufficient, the subject might need to progress to other rescue treatment or procedures listed in Section 6.7. In that case, IMP will be permanently discontinued (see Section 7.2.1).

- In case rescue treatment is initiated at or after Week 16:
  - If the subject experiences intolerable AD signs and/or symptoms during the follow-up period (Week 16 to 32), topical and systemic rescue treatment or procedures listed in Section 6.7 may be prescribed at the discretion of the investigator. In such case, subjects will continue the schedule of trial visits and assessments.

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

Reporting in eCRF

It will be recorded in the eCRF if a medication or procedure is given as rescue treatment.

6.6 Prior and concomitant medication and concurrent procedures

Any medication or vaccine that the subject receives from 3 months (12 months for medications related to AD) prior to screening through the follow-up period 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).
- Dose information, including dose per administration, unit, and frequency.
- Route of administration.

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

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

Investigators may prescribe concomitant medications or procedures to provide adequate supportive care as deemed necessary, except for treatments listed in Section 6.7. The sponsor's medical expert should be contacted if there are any questions regarding concomitant or prior medications and procedures.

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 not violating the exclusion criteria (see Section 5.3) and the list of prohibited medications (Section 6.7).
- Systemic antihistamines and/or anti-infectives.
- Ophthalmic, inhaled, and nasal corticosteroids.

6.7 Prohibited medications and procedures

The medications and procedures listed below are prohibited during the trial from randomization (Week 0). Medications and procedures disallowed prior to randomization are covered by the exclusion criteria (see Section 5.3). In case any prohibited treatments are used during the trial, they must be recorded in the eCRF as concomitant medication.

From randomization through the last follow-up visit (Week 32), the below treatments are prohibited:

1. TCS and TCI.
2. Topical PDE-4 inhibitors.
3. Topical JAK inhibitors.
4. Use of UVA or UVB, PUVA, other phototherapy, tanning beds, or prolonged sun exposure.
5. Systemic corticosteroids (nasal, ophthalmic, and inhaled corticosteroids are allowed).
6. Systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporine, azathioprine), immunomodulating drugs, JAK inhibitors, and retinoids (e.g. alitretinoin).
7. Biological products.
8. Investigational agents other than LEO 138559.
9. Allergen immunotherapy.
10. Live (attenuated) vaccine.
11. Immunoglobulins.
12. Blood products.

Prescription of prohibited medications and procedures in no. 1-6 do not constitute a protocol deviation if given as rescue treatment for AD (Section 6.5). If prohibited medications and procedures are used for reasons other than rescue treatment for AD, they must be recorded as protocol deviations and IMP will be permanently discontinued (see Section 7.2.1).

Please note that receipt of inactive/killed vaccines (e.g. inactive influenza) is allowed, provided that they are not administered within 5 days before/after any trial visit.

6.8 Treatment logistics and accountability

6.8.1 Labelling and packaging of trial products

The IMP will be packaged open-label in individually numbered kits.

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

The labelling of IMPs will be in accordance with the EU Clinical Trial Regulation No 536/2014 Annex VI (66), local regulations, and trial requirements. Label text will be translated into local languages as required.

6.8.2 Storage and accountability of trial products

The investigator or designee must confirm appropriate conditions (e.g. temperature) have been maintained during transit for all IMPs received, and any discrepancies are reported and resolved before use of the IMP.

Only eligible subjects may receive the IMP, and only authorized site staff may supply, prepare, or administer the IMP.

All IMPs must be stored in a secure and restricted area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff and remain in the original container until dispensed.

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

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

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

The investigator or authorized site staff is responsible for IMP accountability, and record maintenance (e.g. receipt, and final disposition records).

Further details regarding storage (including handling of temperature excursions upon receipt or during storage at the trial site) and handling of damaged IMPs (including kits damaged upon receipt) are provided in the trial product handling manual.

6.8.3 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 (full dose, partial dose, or no dose).
- Primary reason for non-compliance: AE, or other (if other, a specification should be provided).

- Date and time of IMP administration (stated for all 3 injections).
- Site of IMP injection: Left/right anterior thigh, left/right abdominal region, left/right upper arm.
- Other: If other, a specification should be provided.

6.8.4 Trial product destruction

All IMP (i.e. used, partly used, and unused vials) must be returned to the CMO, where it will be destroyed according to approved procedures and/or local requirements (**for requirements specific for the UK, see Section 12.5.5**). 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.

6.9 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.

6.10 Reporting product complaints

Any defects or issues with the IMP as well as any device deficiency that has or potentially could have a serious impact on the subject must be reported to the unblinded CRA within 24 hours of knowledge.

(S)AEs which occur due to a defect or issue with the IMP or due to a device deficiency must be reported by the investigator as described in Sections 12.2.4 and 12.2.5.

Examples of product complaints are:

- Device malfunctions and use errors
- Problems with the physical or chemical appearance of the IMP (e.g. particles in the syringe)
- Problems with the packaging material including labelling.

The unblinded CRA will report the product complaint to the Quality department via Global Safety at LEO Pharma within 3 days of first knowledge.

The reporting of the product complaint should contain a detailed description of the defect, issue, or device deficiency, including whether it led to an AE.

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

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

Fax number: +45 6910 2468

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

Additional reporting information can be found on the SAE form.

7 Discontinuation and withdrawal

7.1 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 7.3. Early termination assessments to be conducted for both events are described in Section 7.3.

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

If a subject withdraws from the trial and verbally, or in writing, withdraw their consent to further analysis of samples already taken but not yet tested, the investigator should document this in the subject's medical record and inform LEO Pharma.

Discontinuation of specific sites or of the trial are detailed in Appendix 1 (Section 12.1.10).

7.2 Reasons for discontinuation of IMP

7.2.1 Reasons for permanent discontinuation of IMP

Subjects will permanently discontinue IMP in the event of:

- Evidence of pregnancy, or if the subject is non-compliant with the contraception requirements (see inclusion criterion no. 10).
- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.
- Withdrawal by subject.
- Protocol-specified withdrawal criterion met, defined as initiation of:
  - Any rescue treatment before Week 4.
  - Prohibited medication (except use of rescue treatment with TCS and/or TCI at or after Week 4, see Section 6.5).
- Other reasons, at the discretion of the investigator. If other, a specification should be provided.

For requirements specific for EU countries i.e. CZ, DE, ES, FR, HU, PL and RO, see Section 12.5.1)

Data to be recorded in the 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, e.g.:

- Death.
- Pregnancy.
- AE (if AE, a specification must be provided).
- Lost to follow-up.
- Lack of efficacy.
- Randomized by mistake.
- Withdrawal by subject.
- Protocol-specified withdrawal criterion met.
- Other (if other, a specification should be provided).

In case the primary reason is AE, the AE in question will be linked to the permanent discontinuation of IMP.

7.2.2 Reasons for temporary discontinuation of IMP

In case an urgent situation requires immediate action, IMP dosing may be temporary discontinued if, at the investigator's discretion, 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.

A decision to re-initiate IMP must always be discussed with and approved by the sponsor's medical expert.

7.3 Subject withdrawal from the trial

- A subject may withdraw from the trial at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety or compliance reasons. The subject will be permanently discontinued from the IMP and the trial at that time.
- If the subject withdraws consent for disclosure of future information, LEO Pharma may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

7.4 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 discontinuation of IMP. Subjects should be encouraged to attend all trial visits and be assessed for safety and efficacy according to the schedule of assessments.

For subjects who no longer wish to attend all trial visits, the following visits should be prioritized:

- An early termination visit.
- The primary endpoint visit (16 weeks after randomization).
- A final follow-up visit (18 weeks after last administration of IMP).

Subjects who discontinue IMP but remain in the trial will continue completing the eDiary until the Week 16 visit. The investigator will review any AEs which will be followed up according to Appendix 2 (Section 12.2.4) if the subject agrees.

Withdrawal from trial

Subjects who withdraw/are withdrawn from the trial for any reason should attend an early termination visit as soon as possible after withdrawal. Assessments/procedures to be conducted at this visit are listed in the schedule of trial activities (Section 1.3). If the subject agrees, the investigator will review any AEs which will be followed up according to Section 12.2.4.

Treatment regimen following withdrawal from the trial will be at the investigator's discretion.

Details on data to be recorded in the eCRF for subjects who withdraw from the trial can be found in Section 8.8.

7.5 Lost to follow-up

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

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

- The trial site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to continue in the trial.

- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

8 Trial assessments and procedures

8.1 Overview

Trial procedures and their timing are summarized in the schedule of activities in Section 1.3. Protocol waivers or exemptions are not allowed.

At visits including PRO assessments, the PROs should be completed before any other assessments or procedures. IMP administrations should always occur after all other assessments and procedures planned for the same visit have been performed.

Adherence to the trial design requirements, including those specified in the schedule of activities, is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.

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 experienced in treating AD and have documented experience and/or training in use of the assessments required by the protocol and must be either a physician, a certified physician's assistant, or an advanced registered nurse practitioner (**for requirements specific for CZ, see Section 12.5.2**). All dermatologic assessments must be performed by a dermatologist or an adequately qualified medical doctor.

AEs must be assessed by a physician (see details in Section 10.2).

Immediate safety concerns should be discussed with LEO Pharma immediately upon occurrence or awareness to determine if the subject should continue or discontinue the IMP.

The investigators performing the assessments must not be involved in the administration of IMP (Section 6.3.2).

Data to be collected should follow CDISC controlled terminology whenever it exists (e.g laboratory parameters, questionnaires, ADA, biomarker parameters, anatomical locations, withdrawal reasons, etc.).

8.2 Administrative and baseline procedures

8.2.1 Demographics

The following demographic data will be recorded:

- Date of birth; in general, day, month, and year of birth should be collected. Where it is not allowed to collect the subject's full date of birth, only month and year of birth, or year of birth should be collected as per local legislation.
- Age (years); age (as on the day ICF was signed) must be collected if full date of birth cannot be collected due to local legislations. (If the full date of birth is not collected on the demographics form, age and age unit must be collected on the randomization form.)
- Sex (as determined by the investigator): female, male.
- Ethnic origin (self-reported by the subject): 'Hispanic or Latino', 'not Hispanic or Latino', not reported (not provided or available). **For requirements specific for FR, see Section 12.5.3.**
- Race (self-reported by the subject, more than 1 race may be reported): American Indian or Alaska native, Asian Japanese, Asian Chinese, Asian other, Black or African American, native Hawaiian or other Pacific Islander, White, not reported (not provided or available). **For requirements specific for FR, see Section 12.5.3.**

8.2.2 Medical history

Medical history will be recorded according to the schedule of trial activities (Section 1.3).

In case medical history is incomplete at the screening visit, missing data will be retrieved at Week 0 (baseline).

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

- Atopy history:
  - Date of AD diagnosis.
  - Previous AD treatments (e.g. dupilumab, tralokinumab, lebrikizumab, nemolizumab, JAK inhibitor, methotrexate, cyclosporine, azathioprine), with the following details:
    - Treatment duration.
    - If treatment terminated: reason for termination (e.g. due to insufficient effect or AE).
    - In case of treatment with dupilumab, tralokinumab, lebrikizumab, nemolizumab, or a JAK inhibitor:
      - Received in a trial or as prescription.
  - Asthma.
  - Food allergy.
  - Hay fever.

  - Allergic conjunctivitis
  - Atopic keratoconjunctivitis
  - Eczema herpeticum
- 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.

8.2.3 Body measurement (height)

Height will be recorded according to the schedule of trial activities (Section 1.3).

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

8.2.4 C-SSRS

C-SSRS will be assessed according to the schedule of trial activities (Section 1.3).

The C-SSRS Screening version is a rater-administered instrument used to assess severity of suicidal ideation and suicidal behaviour through a series of simple, plain-language questions (67). The C-SSRS must be completed at the screening visit to check that exclusion criterion no. 12 is not met.

8.2.5 Laboratory assessments

The laboratory assessments conducted at screening are listed in Section 8.4.5.

8.3 Efficacy assessments

8.3.1 EASI

EASI will be assessed by the investigator according to the schedule of trial activities (Section 1.3). At an unscheduled visit, it will be at the discretion of the investigator if EASI should be assessed.

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (68). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. The scoring is based on the Harmonising Outcome Measures for Eczema (http://www.homeforeczema.org/) EASI guidance version 3.

The EASI is a composite index with scores ranging from 0 to 72, with higher values indicating more severe or more extensive condition. The index will be calculated as shown in Panel 7. Briefly, the investigator will assess the severity of 4 AD disease characteristics (erythema, edema/papulation, excoriation, and lichenification) on the 4 body regions (head/neck, trunk, upper extremities, lower extremities); severity will be assessed according to the scale shown in Panel 8. For each body region, a severity sum score will be calculated which will be multiplied by an area score (Panel 8) and by a weighting factor. The EASI score equals the sum of the scores obtained for each body region (Panel 7).

Reporting in eCRF

The body region, severity of the disease characteristics (erythema, edema/papulation, excoriation, and lichenification), and the area score will be recorded in the eCRF. Refer to Appendix 1 (Section 12.1.8) for principles for data entry in the eCRF.

Panel 7: Calculation of the EASI score

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

Abbreviations: AS = area score; EASI = Eczema Area and Severity Index; SS = severity score.
Modified from (69).

Panel 8: EASI severity score scale and area score scale

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

Note: half-points (1.5 and 2.5) are allowed. 0.5 is not permitted.

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

Abbreviations: EASI = Eczema Area and Severity Index.

8.3.2 SCORAD

The SCORAD is a validated tool to evaluate the extent and severity of AD lesions, along with subjective symptoms (70). The maximum total score is 103, with higher values indicating more severe disease. SCORAD will be assessed according to the schedule of trial activities (Section 1.3).

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

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

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

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

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

Note: dryness is evaluated on uninvolved areas.

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

Subjective symptoms (C)
A subjective assessment of the average pruritus and sleep loss over the last 3 days/nights is recorded for each symptom by the subject on a VAS, where 0 is no itching (or no trouble sleeping) and 10 is unbearable itching (or lot of trouble sleeping), with a maximum possible score of 20.

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

Reporting in eCRF
The extent and intensity of disease, as well as the subjective assessment of pruritus and sleep loss, will be reported in the eCRF. Refer to Appendix 1 (Section 12.1.6) for principles for data entry in the eCRF.

8.3.3 vIGA-AD

vIGA-AD will be assessed by the investigator according to the schedule of trial activities (Section 1.3). 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) (71). The vIGA-AD score will be assessed according to the schedule of trial activities (Section 1.3). 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 1 (Section 12.1.8) for principles for data entry in the eCRF.

Panel 9: vIGA-AD

Score	Morphological description
0 - Clear	No inflammatory signs of AD (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.

Abbreviations: AD = atopic dermatitis; vIGA-AD = validated Investigator Global Assessment Scale for Atopic Dermatitis.

8.3.4 BSA involvement

The total BSA affected by AD will be assessed by the investigator for each section of the body as component A of SCORAD (Section 8.3.2) and will be reported as a percentage of all major body sections combined. The following body regions will be assessed (brackets show the highest possible score for each region): head and neck (9%), anterior trunk (18%), back (18%), upper limbs (18%), lower limbs (36%), and genitals (1%). The total BSA score will be assessed according to the schedule of activities (Section 1.3).

The investigator will assess the total AD involvement for the whole body, i.e. head/neck, upper limbs, trunk, genitalia, and lower limbs, 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.

Reporting in eCRF

BSA involvement will be recorded as part of the SCORAD assessment. Refer to Appendix 1 (Section 12.1.8) for principles for data entry in the eCRF.

8.3.5 PROs

8.3.5.1 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. 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 PROs according to the schedule of trial activities (Section 1.3). PROs will either be completed at home (eDiary) or at the trial site (electronic device) (Panel 10).

Panel 10: Overview of PROs to be completed

PROs to be completed at home (eDiary)	PROs to be completed at the trial site (electronic device)
To be completed in the morning[a)] Nocturnal [redacted] (Section 8.3.5.2) Difficulty [redacted] (Section 8.3.5.3) Frequency of [redacted] During the Night (Section 8.3.5.4) **To be completed in the evening**[a)] ADSD (all components) (Section 8.3.5.5)	DLQI (Section 8.3.5.6) POEM (Section 8.3.5.7) EQ-5D-5L (Section 8.3.5.8) WPAI-SHP (Section 8.3.5.9) HADS (Section 8.3.5.10) PGI-S (Section 8.3.5.11) [redacted] ADSD Nocturnal [redacted] Difficulty [redacted] Frequency of [redacted] During the Night PGI-C (Section 8.3.5.12) [redacted] ADSD Nocturnal [redacted] Difficulty [redacted] Frequency of [redacted] During the Night

a) The morning assessments will only be completed until Week 16, the evening assessments will be completed until Week 32.

Abbreviations: ADSD = Atopic Dermatitis Symptom Diary; DLQI = Dermatology Life Quality Index; eDiary = electronic diary; EQ-5D-5L = EuroQol 5-Dimension Health Questionnaire 5 Level; HADS = Hospital Anxiety and Depression Scale; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; POEM = Patient-Oriented Eczema Measure; PRO = patient-reported outcome; WPAI-SHP = Work Productivity and Activity Impairment: Specific Health Problem.

At the screening visit, the subjects will receive an eDiary device and training in using the device. The subjects must start completing the eDiary at least 1 week prior to baseline, but preferably from the date the subjects receive the eDiary. From Week -1 to Week 16, the subjects will be asked to complete the eDiary twice daily, once in the morning and once in the evening. After Week 16, up to Week 32, the subjects will be asked to complete the eDiary in the evening only (Panel 10).

Between Week -1 and Week 32, an e-mail notification alarm will inform the investigator/site staff about non-compliance with eDiary completion. In case of non-compliance, the investigator should remind the subject of the importance of completing the eDiary daily.

Subjects will be asked to return the eDiary at Week 32 or at their last visit in the trial.

8.3.5.2 Nocturnal [redacted] (eDiary)

Nocturnal [redacted] is a single item questionnaire designed developed by LEO Pharma to assess how much the subject [redacted] during the past night. It will be assessed on a 6-point categorical scale (‘none of the night’, ‘a little of the night’, ‘some of the night’, ‘a lot of the night’, ‘all of the night’, ‘I don't know’).

8.3.5.3 Difficulty [redacted] (eDiary)

Difficulty [redacted] is a single item questionnaire designed developed by LEO Pharma to assess the subject’s difficulty to [redacted] the past night. It will be assessed on a 5-point categorical scale (‘not difficult’, ‘a little difficult’, ‘moderately difficult’, ‘extremely difficult’, ‘I don’t know’).

8.3.5.4 Frequency of [redacted] During the Night (eDiary)

Frequency of [redacted] During the Night is a single item questionnaire designed developed by LEO Pharma to assess how many times the subject [redacted] the past night. It will be assessed on a 5-point categorical scale (‘not at all’, ‘[redacted] 1 time’, ‘[redacted] 2 times’, ‘[redacted] 3 times or more’, ‘I don’t know’).

8.3.5.5 ADSD (eDiary)

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

From Week -1 to Week 32, ADSD will be completed by the subject on the eDiary daily. An overview of all PROs, including other PROs collected in the eDiary and PROs collected at the trial site, is presented in Section 8.3.5.1.

8.3.5.6 DLQI (at trial site)

DLQI consists of 10 items addressing the subject’s perception of the impact of their skin disease on different aspects of their quality of life over the past week such as dermatology

related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment. Each item will be scored on a 4 point Likert scale (0='not at all/not relevant', 1='a little', 2='a lot', 3='very much'). The total score (0 to 30) is the sum of the 10 items with higher scores indicating a poorer quality of life (72). The subject will be asked to complete DLQI on an electronic device at the trial site according to the schedule of trial activities (Section 1.3).

8.3.5.7 POEM (at trial site)

POEM consists of 7 items, each addressing a specific symptom (itching, sleep, bleeding, weeping, cracking, flaking, and dryness). The subject will be asked to score how often they experienced each symptom over the past week on a 5 point categorical scale (0='no days', 1='1 to 2 days', 2='3 to 4 days', 3='5 to 6 days', 4='every day'). The total score (0 to 28) is the sum of the 7 items and reflects disease related morbidity with higher scores indicating more severe symptoms (73). The subject will be asked to complete POEM on an electronic device at the trial site according to the schedule of trial activities (Section 1.3).

8.3.5.8 EQ-5D-5L (at trial site)

EQ-5D-5L is a self-administered questionnaire used to assess health status 'today' and is divided into 2 sections. The first section includes 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Each dimension is assessed using a 5-point categorical scale ('no problems', 'slight problems', 'moderate problems', 'severe problems', and 'extreme problems'). The second section consists of a vertical VAS anchored at 0 ('the worst health you can imagine') and 100 ('the best health you can imagine') (74). The subject will be asked to complete EQ-5D-5L on an electronic device at the trial site according to the schedule of trial activities (Section 1.3).

8.3.5.9 WPAI-SHP (at trial site)

WPAI-SHP (v2.0) consists of 6 items and scores can be calculated for 4 domains, each reflecting the percentage impairment due to AD during the past week, with higher scores indicating a greater impairment and lesser productivity (75):

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

The subject will be asked to complete WPAI-SHP on an electronic device at the trial site according to the schedule of trial activities (Section 1.3).

8.3.5.10 HADS (at trial site)

HADS is a 14-item questionnaire with scores ranging from 0 to 21 for anxiety and 0 to 21 for depression. Each of the 14 items will be evaluated on a Likert scale. Scores are considered normal from 0 to 7 and abnormal from 11 to 21 and are categorized as: normal (0 to 7), mild (8 to 10), moderate (11 to 14), and severe (15 to 21) (76). The subject will be asked to complete HADS on an electronic device at the trial site according to the schedule of trial activities (Section 1.3). If the subject presents with symptoms of clinical depression and/or anxiety, the investigator should take appropriate action at their discretion.

8.3.5.11 PGI-S (at trial site)

PGI-S is a questionnaire designed to assess the subject's overall perception of severity. In this trial the severity of [redacted], ADSD, nocturnal [redacted], difficulty [redacted], and frequency of [redacted] during the night over the past week will be evaluated. The subject will be asked to choose 1 option from a 4-point categorical scale as described in Panel 11 (77). The subject will be asked to complete the PGI-S questionnaire on an electronic device at the trial site according to the schedule of trial activities (Section 1.3).

Panel 11: PGI-S

PGI-S	Scale
[redacted] ADSD Nocturnal [redacted] Difficulty [redacted]	'None', 'mild', 'moderate', 'severe'
Frequency of [redacted] During the Night PGI-S	'Never', 'sometimes', 'often', 'very often'

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

8.3.5.12 PGI-C (at trial site)

PGI-C is a questionnaire designed to assess the subject's overall impression of change. In this trial the change in [redacted], ADSD, nocturnal [redacted], difficulty [redacted], and frequency of [redacted] during the night since the subject started treatment will be evaluated. The subject will be asked to choose 1 option from a 5 point categorical scale ('much better', 'a little better', 'no change', 'a little worse', 'much worse') (77). The subject will be asked to complete the PGI-C questionnaire on an electronic device at the trial site according to the schedule of trial activities (Section 1.3).

8.4 Safety assessments

Planned timepoints for all safety assessments are provided in the schedule of activities (Panel 2).

8.4.1 Vital signs

Vital signs (resting BP, pulse, and body temperature) must be assessed prior to IMP administration according to the schedule of trial activities (Section 1.3). Vital signs will be measured in a supine or sitting position following at least 5 minutes of rest, and will include resting blood pressure, pulse, and body temperature. At an unscheduled visit, it will be at the discretion of the investigator if vital signs should be assessed.

In addition, at Weeks 0, 1, 2, 3, and 4, subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken immediately (within 5 minutes) after last IMP administration, after 30 minutes (± 5 minutes), after 1 hour (± 5 minutes), and after 2 hours (± 5 minutes), or until stable, whichever is later **(for requirements specific for EU countries i.e. CZ, DE, ES, FR, HU, PL and RO, see Section 12.5.1)**.

If a subject presents with an abnormal vital sign, the measurement of the vital sign can be repeated approximately 15 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 second 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 first measurement should be recorded in the eCRF. Only the measurement considered true should be recorded in the eCRF, but note that all measured values should be documented in source in these scenarios.

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. 15. 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

It will be recorded in the eCRF if vital signs were measured. The investigator's evaluation ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant') will also be recorded in the eCRF. If vital signs are not measured, a reason should be provided.

Clinically significant abnormal vital signs at screening will be documented as medical history in the eCRF. Any clinically significant worsening of a pre-existing condition or any new clinically significant abnormality occurring after screening will be reported as an AE in accordance with Section 12.2.4.

Refer to Appendix 1 (Section 12.1.8) for principles for data entry in the eCRF.

8.4.2 Physical examination

A physical examination of the subject including general appearance, regional lymph nodes, and dermatologic examination of the skin, must be performed according to the schedule of trial activities (Section 1.3). 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. 15. 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 will be documented as medical history in the eCRF. Any clinically significant worsening of a pre-existing condition or any new clinically significant abnormality after screening will be reported as an AE as described in Section 12.2.4.

Refer to Appendix 1 (Section12.1.8) for principles for data entry in the eCRF.

8.4.3 Body measurement (weight)

Weight will be recorded according to the schedule of trial activities (Section 1.3). The subject's weight (in indoor clothing and without shoes) will be measured (in kg/lb). At an unscheduled visit, it will be at the discretion of the investigator if weight should be measured.

8.4.4 Electrocardiography

ECGs must be measured according to the schedule of trial activities in (Section 1.3). At an unscheduled visit, it will be at the discretion of the investigator if an ECG should be measured.

At each visit, the individual measurement 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 analyze and interpret the ECG data. The ECG service company will provide ECG evaluation reports to the trial sites. The collection and transmission of ECG data will be described in a separate ECG manual.

The investigator must evaluate all abnormal ECG results ('clinically significant' or 'not clinically significant') and sign and date the evaluation. It will be at the discretion of the investigator to take appropriate actions and provide a justification in the medical record.

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 randomized into the trial (respecting exclusion criterion no. 15). If a subject with an abnormal and clinically significant ECG result is randomized, the investigator should provide a justification in the medical record.

Reporting in eCRF

It must be recorded in the eCRF if an ECG was measured. If not, a reason must be provided. 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 findings at the screening visit (or originating from the ECG taken at the screening visit) will be documented as medical history in the eCRF. Any clinically significant worsening of a pre-existing condition or any new clinically significant abnormality occurring after the screening visit will be reported as an AE as described in Section 12.2.4.

Refer to Appendix 1 (Section 12.1.8) for principles for data entry in the eCRF.

8.4.5 Laboratory testing

8.4.5.1 Overview

Blood and urine samples will be collected according to the schedule of trial activities (Section 1.3).

The evaluations shown in Panel 12 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.

Panel 12: Clinical laboratory tests

Clinical chemistry	Hematology
Sodium Potassium Creatinine Urea nitrogen Calcium Alkaline phosphatase AST ALT Gamma glutamyl transferase Lipase Bilirubin[1] (Direct bilirubin)[1] (Indirect bilirubin)[1] Cholesterol LDL cholesterol and HDL cholesterol Triglycerides Tryptase[2]	Hemoglobin Leukocytes Neutrophils Neutrophils/leukocytes[4] Lymphocytes Lymphocytes/leukocytes[4] Monocytes Monocytes/leukocytes[4] Eosinophils Eosinophils/leukocytes[4] Basophils Basophils/leukocytes[4] Thrombocytes
Serology	**Tuberculosis test[3]**
Hepatitis B virus surface antigen[3] Hepatitis B virus surface Ab[3] Hepatitis B virus core Ab[3] Hepatitis C virus Ab[3] HIV-1 Ab[3] and HIV-2 Ab[3] IgE	A tuberculosis test will be performed according to local standard of care for patients requiring initiation of biologic treatment. A tuberculosis test can be performed at the central or local laboratory.
	Serum pregnancy test[3,5]
	Choriogonadotropin Beta

Urinalysis[6]	Urine pregnancy test[5)]
Protein Glucose Ketones Occult blood Leukocytes Nitrite	Choriogonadotropin Beta

1) If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
2) In case of an anaphylactic reaction, analysis of serum tryptase must be performed (please refer to Section 6.2).
3) Conducted at screening. 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 (e.g. HBV-DNA, HCV-RNA).
4) The symbol '/'included in the table represents 'a ratio'.
5) Only women of childbearing potential.
6) The analytes listed will only be measured if the urine dipstick is abnormal.

Abbreviations: Ab = antibody; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL = high density lipoprotein; HIV = human immunodeficiency virus; IgE = immunoglobulin E; LDL = low density lipoprotein.

8.4.5.2 Investigator evaluation of laboratory samples

Laboratory samples sent to the central laboratory

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

In case of an abnormal clinically significant laboratory result at screening and/or baseline, it will be at the discretion of the investigator if the subject should be randomized in the trial in accordance with exclusion criterion no. 15. 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 (e.g. HBV-DNA, HCV-RNA). Subjects with a positive serology, or tuberculosis test at screening should be referred to a competent health care structure for treatment and follow-up.

Serum pregnancy tests for women of childbearing potential will be analyzed by a central laboratory which will provide results to the trial sites. A woman with a positive serum pregnancy test at screening must not be included in the trial (exclusion criterion no. 17).

Instructions 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.

Tests performed at the trial site

Urine samples will be tested with a dipstick according to the schedule of trial activities (Section 1.3). In case of abnormal clinically significant findings, investigator must take appropriate action, at their discretion.

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. The test will be repeated every 4 weeks until Week 20, as well as at Week 32 as shown in the schedule of trial activities (Section 1.3). A woman with a positive urine pregnancy test at Week 0 (baseline) must not be randomized in the trial (exclusion criterion no. 17). A positive urine pregnancy test must be verified with a serum pregnancy test. If the urine pregnancy test is positive but not confirmed by the serum pregnancy test, the subject may continue IMP treatment, but the LEO medical expert should be consulted **(for requirements specific for EU countries i.e. CZ, DE, ES, FR, HU, PL and RO, see Section 12.5.1)**.

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.

Site staff will record in the eCRF if a urine dipstick was performed and whether urinalysis is required for further assessment, as judged by the investigator. If so, a urine sample should be sent to the central laboratory. If the urine sample was not tested with a dipstick, a reason will be provided. In case urinalysis is performed, the investigator's assessment of the results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant') will be recorded in the eCRF.

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 (or originating from laboratory tests taken at the screening visit) will be documented as medical history in the eCRF. Any clinically significant worsening of a pre-existing condition or any new clinically significant abnormality occurring after screening will be reported as an AE as described in Section 12.2.4.

Refer to Appendix 1 (Section 12.1.8) for principles for data entry in the eCRF.

8.4.6 ADA measurements

Blood samples will be collected to determine ADA levels at pre-determined time points according to the schedule of trial activities (Section 1.3). 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 analyzed 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 titer 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.

The ADA results will not be made available to the trial sites during the trial, but will be made available to the investigator upon request after completion of the CTR.

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 1 (Section 12.1.8) for principles for data entry in the eCRF.

8.5 PK assessments

Blood samples for PK assessments will be collected at the time points specified in the schedule of trial activities (Section 1.3). 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 analyzed 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.

LEO Pharma will not provide IMP concentration results to the trial sites during the trial. The results will be available to the investigator upon request after completion of the CTR.

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 1 (Section 12.1.8) for principles for data entry in the eCRF.

8.6 PD assessments

The PD assessments will include:

- Analysis of biomarker expression in serum.

- Analysis of skin swabs to assess *Staphylococcus aureus* abundance and microbiome profile.
- Analysis of skin tape strip samples to assess the molecular profile of the skin (only at selected sites).
- Analysis of skin biopsies to assess biomarker expression. (Skin biopsies will only be collected at a selected number of sites; for subjects who provide informed consent to this component.)

The PD 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 PD/biomarker results will be reported in an addendum to the CTR.

LEO Pharma will not provide biomarker, skin swab, skin tape strip, and skin biopsy results to the trial sites during the trial. The results will be available to the investigator upon request after completion of the CTR.

Biomarker expression in serum
Biomarker expression in serum will be measured to evaluate treatment effect of LEO 138559 on disease biomarkers and biomarkers related to the mechanism of action of LEO 138559.

Blood samples for biomarker analyses will be collected according to the schedule of trial activities (Section 1.3). 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 analyzed include, but are not limited to, IL-13, IL-22, and IL-31.

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

***S. aureus* abundance and microbiome profiling in skin swabs**
Skin swab samples will be collected according to the schedule of trial activities (Section 1.3) to determine *S. aureus* abundance by means of qPCR and additional analysis of microbiome diversity investigated by use of next generation sequencing methods. At an unscheduled visit, it will be at the discretion of the investigator if a skin swab should be collected to determine *S. aureus* abundance and microbiome profiling.

At baseline, standardized swabs will be collected from 3x5 cm skin areas at one lesional area (defined as “swab/strip target lesion”) as well as from an adjacent non-lesional area (the non-lesional area needs to be located between 5 to 20 cm from the lesional area). At baseline visit (Week 0) skin swabs should be taken from both lesional and non-lesional sites. At the

post-baseline visit (Week 16), 1 skin swab will be collected from the original lesion; no skin swab will be collected from non-lesional skin. Skin swabs will be collected from lower limbs, upper limbs, or trunk.

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

Molecular profile of skin tape strip samples
Skin tape strip samples will be collected according to the schedule of trial activities (Section 1.3). Skin tape strips will only be collected at the trial sites selected to collect skin biopsies (see below). At these sites, skin tape strips will be mandatory for all subjects, up to a global cap of 75 subjects.

A maximum of 8 consecutive skin tape strips from paired lesional areas (defined as "swab/strip target lesion") as well as from an adjacent non-lesional area will be collected (the non-lesional area needs to be located between 5 to 20 cm from the lesional area). Tape strips will be collected from lower limbs, upper limbs, or trunk.

At an unscheduled visit, it will be at the discretion of the investigator if a skin tape strip sample should be collected to determine the molecular profile of the skin.

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

Biomarker expression and histology in skin biopsies
Skin biopsies for biomarker expression analysis (RNA analysis) in the skin and for histology will be collected according to the schedule of trial activities (Section 1.3) at selected trial sites only and for subjects who provide informed consent to this component up to a global cap of 75 subjects.

For patients who have consented to participate in the provision of skin biopsies, 5 mm paired lesional and non-lesional biopsies will be collected at baseline (the non-lesional biopsy needs to be located between 5 to 20 cm from the lesional biopsy). At the post-baseline visit, 1 biopsy will be collected from the original lesion; no skin biopsy will be collected from non-lesional skin at the post-baseline visit. Biopsies will be collected from lower limbs, upper limbs, or trunk. Each 5-mm biopsy will be split in 2; 1 part will be used for analysis of RNA, and 1 part will be used for histology/immunohistochemistry/in-situ hybridization. At an unscheduled visit, it will be at the discretion of the investigator if a skin biopsy should be collected.

The biopsy area needs to be separate from the skin swab and tape strip area (unless samples can be taken from a large area).

The biomarkers to be analyzed by histology/immunohistochemistry/in-situ/hybridization include, but are not limited to, the following: markers for inflammation (e.g. S100A9), epidermal markers (e.g. epidermal thickness, keratin type I cytoskeletal 16), and barrier markers (e.g. loricrin).

Collection, handling, and shipment instructions for skin biopsies will be provided in separate laboratory manuals.

Reporting in eCRF
It will be recorded in the eCRF if blood samples, skin swabs, skin tape strips, and skin biopsies were collected. If not collected, a reason should be provided. For skin swabs, skin tape strips, and skin biopsies, it will be recorded if they were collected from lesional or non-lesional skin, and from which body area they were collected.

Refer to Appendix 1 (Section 12.1.8) for principles for data entry in the eCRF.

8.7 Other assessments

8.7.1 Photography (selected sites)

Subjects at selected trial sites will be asked to participate in a voluntary photography component of the trial which involves digital photography assessments to show disease progression over time. Participation in this photography component requires that the subject provides informed consent to this component.

Digital color photographs will be taken of the legs including feet (dorsal and ventral image), torso including arms (dorsal and ventral image), and head and neck (anterior image) according to the schedule of trial activities (Section 1.3). The photographs must always be taken with underwear (modesty garments, provided by the central photography vendor) and female subjects should have their breasts hidden. All faces (eyes and mouth) will be anonymized upon receipt of the images by the central photography vendor. It will be recorded in the eCRF if the photograph(s) was (were) taken; if not, a reason should be provided.

The trial sites will use their own equipment or equipment provided by the photography vendor to take the photographs. Instructions for photography will be provided to the sites in a photography manual. Photography standards and procedures will be provided to the trial sites by the central photography vendor.

The photographs will have no other subject identifier than the subject ID and will be transmitted electronically to the photography vendor using a secure file transfer protocol.

LEO Pharma may at its discretion use the photographs in scientific presentations to other researchers, or in scientific books or journals. The photographs may also be part of material used for training and educational purposes. Steps will be taken to ensure that the identity of the subject is protected by blinding or covering any potential identifying features in the photographs.

8.7.2 Qualitative interviews (selected sites)

Approximately 75 subjects at selected trial sites in CA, DE, PL, UK and US will be asked to participate in a qualitative interview.

Participation in the interview will be part of the local ICF in the relevant countries.

The site personnel will enter the participants' contact details and schedule the interviews at the participants' convenience on a secure IT portal at Week 10 (Visit 10). The site personnel can also request the participants to schedule the interview themselves. In that case a secure link will be sent to the participants' phone via text message and to their email.

Interviews will be conducted by a CRO within 14 days after Week 14 (Visit 12). Subjects who discontinue IMP or withdraw from the trial prior to Week 14 will not be invited to participate in the interviews. Interviews will be conducted in English, German or Polish, depending on the subject's country of residence. Interviews will be conducted via a phone call. Each interview is expected to last approximately 45-60 minutes. A semi-structured interview guide will be used to explore the subjects' experience of participating in the trial, including their experience on therapy and impact on symptoms.

The interview results will be reported separately from the CTR. The coding, analysis and reporting of the interview data will be performed by a CRO based on a separate analysis plan.

The interviewers will be trained in capturing potential AEs. If during the interviews the participant communicates an unreported potential AE, serious or non-serious, it will be reported to the investigator by the interviewer within 24 hours for the investigator to make an assessment and further reporting to the sponsor if needed according to Section 10.

8.8 End of trial

Reporting in eCRF:

End-of-treatment form

An end-of-treatment form will be completed in the eCRF for all subjects who had been exposed to IMP, at the time 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 after having been exposed to IMP (see schedule of trial activities, Section 1.3 and Section 7.3 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 (i.e. did not permanently discontinue IMP prior to Week 16). If not, the primary reason for permanent discontinuation of IMP must be recorded (see Section 7.2.1).

End-of-trial form

An end-of-trial form must be completed in the eCRF for all subjects that have been randomized and/or exposed to treatment. The following data will be collected:

- Did the subject complete the trial (see Section 4.3)? If not, primary reason for not completing the trial will be recorded.
- Date of last contact.
- Primary reason for not completing the trial based on the following categories: Death, pregnancy, AE, lost to follow-up, lack of efficacy, randomized by mistake, withdrawal by subject, or other (if other, please specify).
- Did the subject attend the primary endpoint visit?
- Primary reason for not attending the primary endpoint visit based on the above categories.
- Did the subject attend the follow-up visit?
- Primary reason for not attending follow-up visit based on the above categories.

The end-of-trial form will be completed when the subject has had their last visit (that is, the final follow-up visit [either at Week 32 for subjects who complete the trial or earlier for subjects who permanently discontinue IMP before Week 16 or subjects who withdraw after Week 16] or the early termination visit [for subjects who withdraw from the trial before Week 16]).

8.9 Storage of biological samples

Primary samples (set A samples) for PK will be discarded by the bioanalytical lab upon finalization of the CTR whereas backup samples (set B samples) stored at the central laboratory will be retained no longer than 6 months after completion of the CTR.

Primary samples (set A samples) for ADA evaluation will be discarded by the bioanalytical lab upon finalization of the CTR whereas backup samples (set B samples) stored at the central laboratory will be retained for up to 10 years after final CTR, and then they will be destroyed. Any B samples that have been sent to the bioanalytical lab and used for analysis will also be discarded upon finalization of the CTR. The B samples stored at the central laboratory will be transferred to a central archive facility for long-term storage upon finalization of the CTR.

Any residual PD sample (serum and biopsy) will be stored in a biobank as described below.

Biobank

This protocol includes the collection and analysis of biological samples. If consent is given by the subject, LEO Pharma will store residual serum and biopsy samples collected in a biobank. The biobanked biological samples will be used for future research by LEO Pharma. Donation of the samples for future research is voluntary and subjects must give their written consent to this component to confirm donation and storage and the terms associated herewith. Consent to this component will be recorded in the eCRF.

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 10 years after CTR finalization and will then be destroyed. Results of future research will be reported separately, and individual subject data will not be provided to trial sites unless requested.

9 Scientific rationale for trial design and appropriateness of assessments

9.1 Scientific rationale for trial design

This is a randomized, double-blind, placebo-controlled, multi-site, parallel-group, dose-finding trial, which will be conducted in accordance with the protocol, ICH GCP, and applicable regulatory requirements.

The trial will be conducted at multiple trial sites located in Europe, North America, and Japan.

Patients with AD represent a heterogeneous patient population with disease severity ranging from mild to severe. To mitigate any potential difference in trial outcome based on baseline characteristics, eligibility criteria for inclusion have been carefully selected and trial subjects will be randomized according to a stratified, permuted block design. The randomization will minimize selection bias and ensure that the effect of treatment is not confounded by baseline factors. The stratified permuted block design and the inclusion of prognostic baseline factors in the analysis will improve the precision of the estimated treatment effect.

The most important inclusion criteria for entry into the trial is a diagnosis of AD (as defined at screening by the Hanifin and Rajka 1980 criteria (62)) and history of AD for at least 1 year, to ensure correct diagnosis and rule out differential diagnoses.

Patients with moderate-to-severe AD with inadequate response to treatment with TCS (±TCI as appropriate), or for whom these topical AD treatments are medically inadvisable, are the target population for treatment with LEO 138559. Only adults (aged 18–75 years) are included. In order to evaluate any efficacy of LEO 138559, subjects in the trial cannot be on concomitant medication for AD or have diseases that may influence the evaluation of AD signs and symptoms.

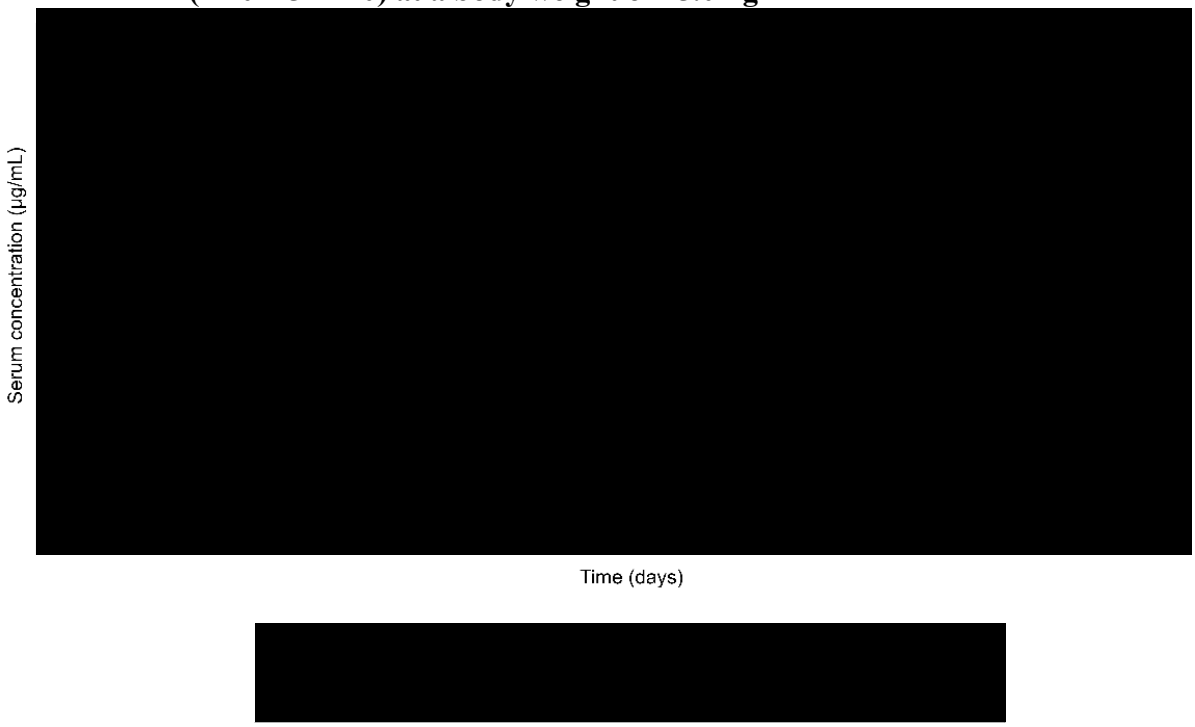
LEO Pharma plans to evaluate LEO 138559 administered SC in 4 different dose regimens. The following LEO 138559 dose regimens will be included:

- Dose regimen 1: LEO 138559 [redacted] mg SC Weeks 0, 1, 2, 3 and then [redacted] mg SC Q2W from Week 4.
- Dose regimen 2: LEO 138559 [redacted] mg SC Weeks 0, 1, 2 and then [redacted] mg SC Q2W from Week 4.
- Dose regimen 3: LEO 138559 [redacted] mg SC Weeks 0 and 2 and then [redacted] mg SC Q2W from Week 4.
- Dose regimen 4: LEO 138559 [redacted] mg SC Weeks 0 and 2 and then [redacted] mg SC Q2W from Week 4.

The dose regimens selected for the trial are based on the PK data from the FiH phase 1 (LP0145-1315) trial, a phase 1 (LP0145-1486) trial, and a phase 2a trial (LP0145-1376) pooled in a population PK model. The efficacy data from these trials have also been used to guide the dose selection, and the preliminary PK/PD model suggests correlation between [redacted], exposure, and response. Due to the limited data from the phase 2a trial, a subgroup analysis based on [redacted] is associated with high uncertainty, but the data suggest that [redacted] subjects [redacted] would benefit from a higher dose than in the phase 2a trial (LP0145-1376, 450 mg Q2W). No safety concern is thought to be associated with higher exposure in [redacted] subjects, as only mild and moderate AEs have been observed in the completed clinical trials and there was no apparent correlation between exposure and AEs. The rationale for the dose selection is also described and summarized in a separate document that also includes details of the population PK model (78).

Based on the available efficacy and safety data from completed clinical trials and in order to identify a dose which can provide maximum efficacy in this patient population, a dose regimen of [redacted] mg loading dose at Week 0, 1, 2, 3 (to reach steady-state concentrations faster), followed by [redacted] mg Q2W dosing from Week 4 onwards (dose regimen 1) is included in the planned phase 2b trial. With this dose regimen, it is predicted that maximum serum concentration (C_{max}) will be reached by Week 4 [redacted] µg/mL in a 75-kg subject) (Panel 13). The predicted average C_{max} is below the maximum observed serum concentrations in the phase 2a trial (LP0145-1376).

Panel 13: Simulated serum concentrations of LEO 138559 in the phase 2b trial (LP0145-2240) at a body weight of 75.0 kg



Simulated serum concentrations for the 4 dose regimens in the phase 2b trial for a subject with a body weight of 75.0 kg. The red dashed line indicates the maximum observed concentration in the phase 2a trial (µg/mL).
Abbreviations: Q2W = every 2 weeks; W = Week.

The dosing of mg Q2W in dose regimen dose regimen used in the phase . In the phase demonstrated a statistically significant difference in favor of LEO 138559 compared to placebo with regards to change in EASI score from baseline to Week 16, and it was shown to be well tolerated. With this dose regimen, steady-state concentration is predicted to be reached by Week 14 (µg/mL in a 75-kg subject) (Panel 13).

Dose regimens 3 and 4 have been included to provide a 2- and 4-fold lower exposure compared to the dose regimen 1, respectively. This is to provide a sufficient difference in exposure between the dose regimens to allow for a meaningful comparison of efficacy, and to secure that the dose regimens cover a sufficient exposure range to investigate a dose exposure response relationship. It will also allow for testing the impact of possible covariates, such as body weight, on the response.

A treatment duration of 16 weeks was chosen to ensure capturing a maximal effect of the active compound, LEO 138559, after exposure steady state is reached. Based on phase 2a

data, the clinical efficacy steady state for EASI-75 is anticipated to have been reached by Week [redacted]. The 18 weeks of follow-up after the last active IMP administration at Week 14 (corresponding to 16 weeks after the end of the treatment period at Week 16), is based on [redacted] half-lives for LEO 138559 ($t_{1/2}$ between [redacted] days).

The trial endpoints have been selected to evaluate the efficacy of LEO 138559 in improving the severity and extent of AD. EASI and vIGA-AD will be used in this clinical trial as investigator-rated assessments of disease severity. EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (68, 79). vIGA-AD is a validated instrument used in clinical trials to assess the subject's global AD. The primary endpoint of the trial is to evaluate the percent change in EASI score from baseline to Week 16. The trial endpoints will also address subject's perception of disease severity and the impact on sleep, daily activity, and HRQoL, and safety.

9.2 Appropriateness of assessments

Efficacy assessments

EASI, SCORAD, and vIGA-AD are validated measures used in clinical trials by investigators to assess the severity and/or extent of AD (see Sections 8.3.1, 8.3.2, and 8.3.3) (68-71).

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 signs and symptoms of AD (including itch) and HRQoL (Section 8.3.5).

Safety assessments

Standard clinical methods of subject evaluations, such as AE monitoring (Section 10), vital signs, physical examination, ECG, laboratory testing including pregnancy testing, and ADA will be used to assess subject safety (Section 8.4). Given some large proteins may cause indirect adverse cardiac effects upon long-term exposure, data on ECG will be collected and evaluated (Section 8.4.4). Data on ADA will be collected in order to evaluate the potential immunogenicity of LEO 138559 (Section 8.4.6).

PK assessments

Serum concentration of LEO 138559 will be measured to further characterize the PK of LEO 138559 in subjects with moderate-to-severe AD (Section 8.5). The serum concentrations will be summarized 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.

PD assessments

Biomarkers in serum will be evaluated to assess the molecular response of LEO 138559 on inflammatory processes in AD in general, and more specifically on the IL-22 pathway. The collection of skin tape strips (mandatory for subjects at selected sites) and biopsies (volunteer subjects at selected sites) permits the exploratory analysis of the effect of LEO 138559 treatment on cutaneous features of AD and in particular the IL-22 pathway. The collection of skin swabs will allow to capture the impact of LEO 138559 treatment on *S. aureus* abundance and the microbiome profile. All PD assessments aim at exploring the mechanism of LEO 138559 and to potentially identify sub-populations of AD subjects with increased response to treatment.

10 AE, SAE, and other safety reporting

AEs and SAEs are defined in Appendix 2 (Section 12.2).

10.1 Time period and frequency of collecting AE information

All AEs will be collected from the signing of the ICF until end-of-trial (defined as the last visit in the trial), at the timepoints specified in the schedule of activities (Section 1.3). Pre-existing conditions (including those found as a result of screening procedures) will be recorded as medical history.

The timing of AE start (i.e. whether prior to or after IMP administration) will be recorded in the eCRF as described in Appendix 2 (Section 12.2.4).

All SAEs will be recorded and reported to LEO Pharma immediately without undue delay but no later than within 24 hours of awareness, as indicated in Appendix 2 (Section 12.2.5). The investigator will submit any updated SAE data to LEO Pharma within 24 hours of it being available.

10.2 Method of detection AEs

AEs must be assessed by a physician.

Care will be taken not to introduce bias when detecting AEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

At all visits, the subject will be asked a non-leading question by the investigator about AEs, e.g.: “How have you felt since I saw you last?” 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 8.4.1 to 8.4.5.

10.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow-up with the subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.5). Further information on follow-up procedures is given in Appendix 2 (Section 12.2.4).

10.4 Regulatory reporting requirements for SAE

Prompt notification (within 24 hours, see Appendix 2 [Section 12.2.5]) by the investigator to LEO Pharma of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial treatment under clinical investigation are met.

LEO Pharma has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial treatment under clinical investigation.
LEO Pharma will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from LEO Pharma will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

All SAEs that occur during the trial until the last safety follow-up visit, whether considered to be associated with the IMP or not, must be reported to LEO Pharma on the (paper) SAE form immediately, without undue delay and no later than within 24 hours of obtaining knowledge.

The completed SAE forms must be faxed or scanned and e-mailed to Global Safety at LEO Pharma. Contact details are given as described in Appendix 2 (Section 12.2.5).

Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

10.5 Pregnancy

Details of all pregnancies will be collected after first exposure to IMP and until the subject has completed the trial. The pregnancy must be reported to LEO Pharma within 24 hours of first knowledge using the (paper) pregnancy form (part I). All pregnancies must be followed up until delivery or termination, and outcome must be reported on the (paper) pregnancy form (part II) within 24 hours of first knowledge.

The completed pregnancy forms must be faxed or scanned and e-mailed to Global Safety at LEO Pharma. Contact details are given in Appendix 2 (Section 12.2.5).

Pregnant subjects must immediately discontinue IMP permanently (Section 7.2.1).

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs and will be reported as such. For SAE definitions, see Appendix 2 (Section 12.2.2).

The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to LEO Pharma.

Any post-trial pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to LEO Pharma as described in Section 10.4. While the investigator is not obligated to actively seek this information about former trial subjects, he or she may learn of an SAE through spontaneous reporting.

10.6 Other events that require expedited reporting

Not applicable.

10.7 Reporting of other events

10.7.1 AEs of special interest

Eczema herpeticum is considered an AESI. If available (e.g. as part of the standard clinical practice), the below additional skin findings are to be recorded in the eCRF:

- Lesion type (papules, vesicles, crusts, eroded pits, other).
- Disseminated/localized.
- Location (face, scalp, back, chest, upper limb, lower limb, genitals).
- Present in an area with visible eczema / no visible eczema / present in areas with and without eczema.
- Monomorphic/polymorphic.
- Confirmation of herpes simplex virus (not confirmed, PCR, viral culture, Tzanck, other).

10.7.2 Medication error

Medication error refers to any unintentional error in the dispensing or administration of an IMP.

Medication errors include accidental overdose or underdose, inappropriate schedule of product administration, 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. See also Section 6.8.3 for recording of treatment non-compliance.

Medication error must be recorded on the Other Events Involving IMP form in the eCRF. In addition, any clinical consequences of the medication error must be recorded as separate AEs on the AE form. If the AE originating from the medication error qualifies as an SAE, expedited reporting is required (Appendix 2, [Section 12.2.5]).

If the medication error is due to a device deficiency, the device deficiency must be reported as a product complaint as described in Section 6.10.

11 Statistical considerations

11.1 Sample size

A total of 250 subjects, including at least 25 Japanese subjects will be randomized in a 1:1:1:1:1 ratio to 1 of the 5 treatment regimens outlined in Section 6.2.

The sample size is chosen, based on the results of a simulation. The simulation assessed the power to reject the null hypotheses included in the testing hierarchy specified in Section 11.3.6. Additionally, the simulation was used to discern, for which effect sizes, the trial would have approximately 50% power to detect a significant difference, in the mean percent change from baseline in EASI score at Week 16 between dose regimens 1 and 2, at the 5% significance level.

The percent change from baseline was simulated in a 4-step process. First, baseline EASI scores were obtained by resampling from a large phase 3 development program in moderate-to-severe AD. Next, the change from baseline was simulated for each subject under a multivariate normal assumption. The assumed mean change from baseline in EASI score from Week 1 to 16 was based on a component related to the effect of treatment, provided in Panel 14 for all 5 dose regimens and an effect related to the baseline EASI score for each assessment.

Panel 14: Assumed values for the mean change from baseline in EASI score from Week 1 to Week 16

	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16
Dose regimen 1	-6.8	-10.3	-13.8	-17.3	-19.6	-18.8	-18.2	-17.8	-19.3	-20.7
Dose regimen 2	-5.0	-7.6	-10.2	-12.8	-14.5	-13.9	-13.5	-13.2	-14.3	-15.3
Dose regimen 3	-5.0	-6.8	-9.2	-11.5	-13.1	-12.5	-12.2	-11.9	-12.9	-13.8
Dose regimen 4	-3.3	-5.0	-6.6	-8.3	-9.4	-9.0	-8.8	-8.6	-9.3	-10.0
Placebo	-1.9	-3.8	-4.2	-4.6	-5.4	-3.8	-4.6	-5.4	-4.5	-3.5

Abbreviations: Wk = Week.

The assumptions for the placebo and dose regimen 2 groups are based on the observed data from the phase 2a proof-of-concept trial. Based on PK/PD modeling, it is anticipated that dose regimens 3 and 4 will retain approximately 90% and 65% of the mean change from baseline in EASI score observed for dose regimen [redacted] in the phase [redacted] trial. For dose regimen 1, the mean change from baseline in EASI score from Week 1 to Week 16 is assumed to have an additional reduction of 35% compared to dose regimen 2.

The covariance matrices for the 5 dose regimens in the simulation were assumed to be equal and have a compound symmetry structure with variances equal to 111.0 and covariances equal to 32.5.

The third step was to ensure that the underlying EASI scores from Week 1 to 16 were within the range of the EASI score scale, which runs from [0,72]. This implies natural bounds for the individual simulated changes from baseline in EASI score, as they must lie within the interval, [-baseline score, 72-baseline score].

The final step was to derive the percent change from baseline in EASI score from Week 1 to Week 16, by dividing the simulated changes in baseline in EASI score from Week 1 to 16 by the subject's baseline EASI score.

The simulation further assumed that percentage of subjects withdrawing or experiencing an intercurrent event by Week 16 in dose regimens 1-4 and placebo arms are 20%, 20%, 30%, 40%, and 40%, respectively, the timing of which was assumed to be exponentially distributed.

To approximate the power, 1,000 data sets with 250 subjects were generated based on the randomization scheme. For each data set, 100 complete versions were generated by imputing missing data separately for each treatment arm. The baseline and all post-baseline EASI assessments were included in the imputation model. The imputed data sets were analyzed based on an ANCOVA model. The pooled estimate of the difference in the LSmean change from baseline, along with the associated 95% Cis and nominal p-values, were derived for each simulated data set by applying Rubin's rules to the estimates and standard errors from the ANCOVA analysis of the imputed datasets.

Panel 15 provides the nominal power as well as the prioritized power based on the hierarchical testing procedure, to reject the null hypotheses testing the LEO 138559 dose regimens 1-4 versus placebo, with respect to the differences in the mean percent change in EASI score from baseline to Week 16.

Panel 15: Approximate nominal and prioritized power for rejecting the null hypotheses including in the testing hierarchy, based on the results of the simulation

Hypothesis	Nominal power	Prioritized power
Dose regimen 1 vs Placebo	~100%	~100%
Dose regimen 2 vs Placebo	99.1%	~99.1%
Dose regimen 3 vs Placebo	97.2%	~96.4%
Dose regimen 4 vs Placebo	67.4%	~65.0%
Dose regimen 1 vs 2	49.7%	NA

Note: ~100% power refers to scenarios in which the associated null hypothesis was rejected in each of the 1,000 simulated trials.

Abbreviations: NA = not applicable.

11.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All subjects randomized will be included in the FAS and will be analyzed for efficacy based on the planned (randomized) treatment allocation. 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 randomized subject from the FAS, a justification addressing ICH E9 will be given.

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

A PK analysis set will be defined as all subjects who received at least 1 dose of LEO 138559 and have at least 1 quantifiable PK sample.

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

11.3 Statistical analysis

11.3.1 General principles

Baseline measurements are defined as the latest available observation at or prior to the date of the first IMP administration, unless otherwise specified.

All significance tests will be two-sided using the 5% significance level. All CIs will be presented with 95% degree of confidence, unless otherwise specified. LSmeans will be estimated using the observed margins for the FAS.

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

Categorical data will be summarized using the number and percentage of subjects in each category and treatment group. Continuous data will be summarized using the mean, SD, median, 1st quartile and 3rd quartile, minimum, and maximum values.

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

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

Unless otherwise stated, efficacy analyses will be performed based on the FAS, safety analyses will be based on the safety analysis set, and PK analyses will be based on the PK analysis set.

11.3.2 Handling of missing values

The methods for handling of missing values for the efficacy endpoints are described in Sections 11.3.7, 11.3.8, and 11.3.9.

11.3.3 Disposition of subjects

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

11.3.4 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomized subjects and by treatment group. Presentations of age, sex, ethnicity, race, and baseline EASI score by treatment group will also be given by baseline disease severity (baseline vIGA-AD score), region (Japan, Other countries), prior use of biologics or systemic JAK inhibitors for AD (Yes/No), and baseline biopsy status (willingness to provide biopsies: Yes/No).

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

11.3.5 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 summarized 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.

11.3.6 Testing strategy

The following hierarchical procedure will be used to ensure strong control of the familywise error rate at the 5% significance level (two-sided significance tests), when testing the null hypotheses associated with the primary endpoint, percent change in EASI score from baseline to Week 16:

1. LEO 138559 [redacted] mg SC Weeks 0, 1, 2, 3 and then [redacted] mg Q2W from Week 4 (dose regimen 1) versus placebo.
2. LEO 138559 [redacted] mg SC Weeks 0, 1, 2 and then [redacted] mg Q2W from Week 4 (dose regimen 2) versus placebo.
3. LEO 138559 [redacted] mg SC Weeks 0 and 2 and then [redacted] mg Q2W from Week 4 (dose regimen 3) versus placebo.
4. LEO 138559 [redacted] mg SC Weeks 0 and 2 and then [redacted] mg Q2W from Week 4 (dose regimen 4) versus placebo.

Under the hierarchical procedure, the first null hypothesis (the difference in the mean percent change in EASI score from baseline to Week 16 between dose regimen 1 and placebo is equal to 0), is tested at the 5% significance level. If that null hypothesis is rejected, the procedure will proceed to test null hypothesis 2 at the 5% significance level. However, if the first null hypothesis cannot be rejected, the procedure stops and null hypotheses 2-4 will not be formally tested. The procedure continues in this fashion, until it either encounters a null hypothesis that cannot be rejected, or all null hypotheses have been rejected. For the purposes of the hierarchical testing procedure, the hypothesis tests will be based on the analysis of the primary estimand for the primary endpoint.

11.3.7 Estimand strategy

The estimand strategy is specified in terms of the variable type, e.g. continuous, binary/categorical, and time-to-event. A primary analysis will be pre-specified for each

estimand and pre-specified sensitivity analyses will be conducted to assess the robustness of the results with respect to departures from the statistical assumptions of the primary analysis.

Description of intercurrent events

An intercurrent event refers to a post-baseline event that affects either the interpretation or the existence of the measurements of an endpoint. For the purposes of this trial, we define the following 2 intercurrent events:

- ***Initiation of rescue treatment:*** This event occurs when a subject initiates rescue treatment as listed in no. 1-6 of Section 6.7 for intolerable AD signs and/or symptoms. The timing of the event will be taken as the date of initiation of the rescue treatment recorded in the eCRF.
- ***Permanent discontinuation of IMP:*** This event occurs when a subject permanently discontinues IMP. This event can occur either at the subject's own initiative or at the investigator's or sponsor's discretion. The timing of the event will be taken as the date of permanent discontinuation of IMP as recorded in the eCRF.

Panel 16 provides an overview of the estimand strategies defined in Sections 11.3.7.1, 11.3.7.2, and 11.3.7.3 that will be used to address occurrences of the intercurrent events described above.

An overview of statistical analysis of endpoints can be found in Panel 17.

Panel 16: Handling of observed and missing data according to intercurrent events in the primary analysis of the estimands defined in Sections 11.3.7.1, 11.3.7.2, and 11.3.7.3

Events	Observed data or missing	Continuous endpoints			Binary endpoints		TTE endpoints
		Primary Estimand	Hypothetical Suppl. Estimand	Second Suppl. Estimand	Primary Estimand	Suppl. Estimand	Primary Estimand
Initiation of rescue treatment	Observed	Treated as missing, MI	Treated as missing, MI	Value will be used as observed	NRI	Value will be used as observed	Not applicable
	Missing	MI	MI	MI	NRI	MI	Not applicable
Permanent discontinuation of IMP, for reasons other than lack of efficacy or an AE related to worsening of AD	Observed	Treated as missing, MI	Treated as missing, MI	Value will be used as observed	Treated as missing, MI	Value will be used as observed	Accounted for as a competing risk[a]
	Missing	MI	MI	MI	MI	MI	Accounted for as a competing risk[a]
Permanent discontinuation of IMP, due to lack of efficacy or an AE related to worsening of AD	Observed	Treated as missing, LOCF	Treated as missing, MI	Value will be used as observed	NRI	Value will be used as observed	Accounted for as a competing risk[a]
	Missing	LOCF	MI	MI	NRI	MI	Accounted for as a competing risk[a]

Events	Observed data or missing	Continuous endpoints			Binary endpoints		TTE endpoints
		Primary Estimand	Hypothetical Suppl. Estimand	Second Suppl. Estimand	Primary Estimand	Suppl. Estimand	Primary Estimand
No intercurrent events	Observed	Value will be used as observed	Value will be used as observed	Value will be used as observed	Value will be used as observed	Value will be used as observed	Not applicable
	Missing	MI	MI	MI	MI	MI	Not applicable

a) Withdrawal from trial will also be accounted for as a competing risk.
Abbreviations: AD = atopic dermatitis; AE = adverse event; IMP = investigational medicinal product; LOCF = last observation carried forward; MI = multiple imputation; NRI = non-responder imputation; Suppl. = supplementary; TTE = time-to-event.

Panel 17: Statistical analysis of endpoints

Endpoint	Estimands to be analyzed
Percent change in EASI score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints. Second supplementary estimand for continuous endpoints.
Achievement of EASI-50 at Week 16.	Primary estimand for binary endpoints. Supplementary estimand for binary endpoints.
Achievement of EASI-75 at Week 16.	Primary estimand for binary endpoints. Supplementary estimand for binary endpoints.
Achievement of EASI-90 at Week 16.	Primary estimand for binary endpoints. Supplementary estimand for binary endpoints.
Achievement of EASI-100 at Week 16.	Primary estimand for binary endpoints. Supplementary estimand for binary endpoints.
Change in EASI score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Change in SCORAD score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Percent change in SCORAD score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Achievement of vIGA-AD score of 0 (clear) or 1 (almost clear) at Week 16.	Primary estimand for binary endpoints. Supplementary estimand for binary endpoints.
Change in BSA from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Percent change in BSA from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Reduction of ADSD Worst [redacted] score (weekly average) ≥4 from baseline to Week 16.	Primary estimand for binary endpoints. Supplementary estimand for binary endpoints.
Change in DLQI (and individual domain scores) from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Percent change in DLQI (and individual domain scores) from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Change in POEM score (and individual item scores related to itch and sleep) from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.

Endpoint	Estimands to be analyzed
Percent change in POEM score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Change in EQ-5D-5L index score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Percent change in EQ-5D-5L index score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Change in EQ-5D-5L VAS score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Percent change in EQ-5D-5L VAS score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Change in HADS score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Percent change in HADS score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Change in Difficulty [redacted] (weekly average) from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Percent change in Difficulty [redacted] (weekly average) from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Change in Nocturnal [redacted] (weekly average) from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Percent change in Nocturnal [redacted] (weekly average) from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Change in Frequency of [redacted] During the Night (weekly average) from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Percent change in Frequency of [redacted] During the Night (weekly average) from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Change in WPAI-SHP domain scores from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.

Endpoint	Estimands to be analyzed
Percent change in WPAI-SHP domain scores from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Change in SCORAD Part C (Pruritus VAS) score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Percent change in SCORAD Part C (Pruritus VAS) score from baseline to Week 16.	Primary estimand for continuous endpoints. Hypothetical supplementary estimand for continuous endpoints.
Time from baseline to use of any rescue treatment.	Primary estimand for time-to-event endpoints. Supplementary estimand for time-to-event endpoints
Reduction of ADSD Worst [redacted] score (weekly average) ≥4 from baseline to Week 16.	Baseline subgroup estimand.
Reduction of DLQI ≥4 from baseline to Week 16.	Baseline subgroup estimand.
Reduction of POEM ≥4 from baseline to Week 16.	Baseline subgroup estimand.

Abbreviations: ADSD = Atopic Dermatitis Symptom Diary; BSA = body surface area; DLQI = Dermatology Life Quality Index; 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; EASI-100 = 100% reduction in EASI score; EQ-5D-5L = EuroQoL 5 Dimension Health Questionnaire 5 Level; HADS = Hospital Anxiety and Depression Scale; POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; VAS = Visual Analogue Scale; vIGA-AD = validated Investigator Global Assessment Scale for Atopic Dermatitis; WPAI-SHP = Work Productivity and Activity Impairment: Specific Health Problem.

11.3.7.1 Estimands for continuous endpoints

The primary and hypothetical supplementary estimands for continuous endpoints, which differ only in handling of the missing data, attempt to quantify the effect of treatment, in the hypothetical scenario, where subjects do not permanently discontinue IMP for any reason and where rescue treatment is not made available.

The estimands are described by the following attributes:

A. Target Population: Subjects with moderate-to-severe AD, as defined through the inclusion and exclusion criteria listed in Section 5.

B. Variable: Applied to continuous endpoints.

C. Treatment conditions: LEO 138559 dose regimens 1-4 versus placebo.

D. Strategies for handling intercurrent events:

a. For subjects requiring the use of rescue treatment or permanently discontinuing IMP, the hypothetical strategy will be used to estimate the treatment effect in the hypothetical scenario where rescue treatment is not available, and where subjects do not permanently discontinue IMP for any reason.

E. Population level summary: Difference in means between the treatment conditions.

Second supplementary estimand

The second supplementary estimand for continuous endpoints attempts to quantify the effect of the decision to treat subjects with the randomized treatment, ignoring the occurrence of intercurrent events.

The estimand is described by the following attributes:

A. Target Population: Subjects with moderate-to-severe AD, as defined through the inclusion and exclusion criteria listed in Section 5.

B. Variable: Applied to percent EASI change from baseline endpoints.

C. Treatment conditions: LEO 138559 dose regimens 1-4 versus placebo.

D. Strategies for handling intercurrent events

a. The treatment policy strategy will be used to handle the initiation of rescue treatment or permanent discontinuation of IMP. Data observed after the occurrence of such events will be included in the analysis.

E. Population level summary: Difference in means between the treatment conditions.

11.3.7.2 Estimands for binary endpoints

The primary estimand for binary endpoints attempts to quantify the effect of treatment in the hypothetical scenario where:

- All subjects remain on treatment except for those permanently discontinuing IMP due to lack of efficacy or the occurrence of an AE related to worsening of AD. AEs considered related to worsening of AD will be specified in the SAP.

The occurrence of the following intercurrent events will be treated as indicating a failure of the randomized treatment:

- Permanent discontinuation of IMP due to lack of efficacy or the occurrence of an AE related to worsening of AD.
- Initiation of rescue treatment.

The estimand is described by the following attributes:

A. Target Population: Subjects with moderate-to-severe AD, as defined through the inclusion and exclusion criteria listed in Section 5.

B. Variable: Applied to binary endpoints.

C. Treatment conditions: LEO 138559 dose regimens 1-4 versus placebo.

D. Strategies for handling intercurrent events

   a. Subjects initiating rescue treatment or permanently discontinuing IMP due to lack of efficacy or the occurrence of an AE related to worsening of AD are defined as treatment failures according to the composite strategy.

   b. For subjects permanently discontinuing IMP due to reasons other than lack of efficacy or the occurrence of an AE related to worsening of AD, the hypothetical strategy will be used to estimate the effect of treatment in the hypothetical scenario where subjects do not permanently discontinue IMP for reasons other than lack of efficacy or the occurrence of an AE related to worsening of AD.

E. Population level summary: Difference in response rates between the treatment conditions.

Supplementary estimand

The supplementary estimand for binary endpoints attempts to quantify the effect of the decision to treat subjects with the randomized treatment, ignoring the occurrence of intercurrent events.

The estimand is described by the following attributes:

A. Target Population: Subjects with moderate-to-severe AD, as defined through the inclusion and exclusion criteria listed in Section 5.

B. Variable: Applied to EASI, vIGA-AD and ADSD Worst [redacted] responder endpoints.

C. Treatment conditions: LEO 138559 dose regimens 1-4 versus placebo.

D. Strategies for handling intercurrent events:

    a. The treatment policy strategy will be used to handle the initiation of rescue treatment or permanent discontinuation of IMP. Data observed after the occurrence of such events will be included in the analysis.

E. Population level summary: Difference in response rates between the treatment conditions.

11.3.7.3 Estimands for time-to-event endpoints

The primary estimand for the time-to-event endpoint, time from baseline to the initiation of rescue treatment, quantifies the effect of treatment while subjects are receiving treatment.

The estimand is described by the following attributes:

A. Target Population: Subjects with moderate-to-severe AD, as defined through the inclusion and exclusion criteria listed in Section 5.

B. Variable: Time from baseline to the initiation of rescue treatment.

C. Treatment conditions: LEO 138559 dose regimens 1-4 versus placebo.

D. Strategies for handling intercurrent events:

    a. Subjects permanently discontinuing IMP are considered to have experienced a competing risk, i.e. no longer considered at risk for initiating rescue treatment, in line with the while on treatment strategy.

E. Population level summary: Difference in the cumulative incidence of initiation of rescue treatment at Week 16 between the treatment conditions.

Supplementary estimand

The supplementary estimand assesses the effect of the treatment on the composite endpoint, time from baseline to the initiation of rescue treatment or permanent discontinuation of IMP, whichever occurs first.

The estimand is described by the following attributes:

A. Target Population: Subjects with moderate-to-severe AD, as defined through the inclusion and exclusion criteria listed in Section 5.

B. Variable: Time from baseline to the initiation of rescue treatment or permanent discontinuation of IMP, whichever occurs first.

C. Treatment conditions: LEO 138559 dose regimens 1-4 versus placebo.

D. Strategies for handling intercurrent events:

    a. For subjects who permanently discontinue IMP prior to the initiation of rescue treatment, the event-time is taken as the time of permanent discontinuation of IMP according to the composite time to event variable defined above.

E. Population level summary: Difference in the cumulative incidence at Week 16 between the treatment conditions.

11.3.7.4 Baseline subgroup estimands

The baseline subgroup estimands are identical to the primary binary estimand but restricted to subgroups, and are described by the following attributes:

A. Target Population: Subjects with moderate-to-severe AD, as defined through the inclusion and exclusion criteria listed in Section 5 with:

    a. Having a weekly average ADSD Worst [redacted] score of ≥ 4 at baseline.

    b. Having a DLQI score of ≥ 4 at baseline.

    c. Having a POEM score of ≥ 4 at baseline

B. Variable:

    a. Reduction of ADSD Worst [redacted] score (weekly average) ≥ 4 from baseline to Week 16.

    b. Reduction of DLQI ≥ 4 from baseline to Week 16.

    c. Reduction of POEM score ≥ 4 from baseline to Week 16.

C. Treatment conditions: LEO 138559 dose regimens 1-4 vs placebo.

D. Strategies for handling intercurrent events:

a. Subjects initiating rescue treatment or permanently discontinuing IMP due to lack of efficacy or the occurrence of an AE related to worsening of AD are defined as treatment failures according to the composite strategy.

b. For subjects permanently discontinuing IMP due to reasons other than lack of efficacy or the occurrence of an AE related to worsening of AD, the hypothetical strategy will be used to estimate the effect of treatment in the hypothetical scenario where subjects do not permanently discontinue IMP for any reason.

E. Population level summary: Difference in response rates between the treatment conditions.

11.3.8 Primary estimand analysis

11.3.8.1 Analysis of primary estimand for continuous endpoints

Primary analysis

Data collected after permanent discontinuation of IMP or after initiation of rescue treatment will be excluded from the analysis and "treated as missing". Missing data and data "treated as missing" will be split into two groups:

1. Data "treated as missing" due to permanent discontinuation of IMP due to lack of efficacy, an AE related to worsening of AD, or rescue treatment.
2. Missing data or data "treated as missing" for other reasons than permanent discontinuation of IMP due to lack of efficacy, an AE related to worsening of AD, or rescue treatment.

The first group will have their missing values imputed using last observation carried forward. This reflects an assumption that subjects that need rescue treatment or permanently discontinue IMP due to lack of efficacy or an AE related to worsening of AD must be expected not to improve going forward even if they had continued IMP.

The second group will be imputed using MI (100 iterations) under a MAR assumption within each treatment group. All subject-level data observed prior to the occurrence of an intercurrent event will be used to inform the imputation models. Further details regarding the specification of the imputation models, including choice of seed, will be specified in the SAP.

The imputed datasets will be combined to create 100 complete datasets. For each of the 100 complete datasets, the response will be analyzed using an ANCOVA model adjusted for treatment, baseline disease severity (baseline vIGA-AD score), region (Japan, Other

countries), and prior use of biologics or systemic JAK inhibitors for AD (Yes/No). The model will also be adjusted for the baseline value of the dependent variable.

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

Sensitivity analysis
A sensitivity analysis will be performed for the change and percent change in EASI score from baseline to Week 16 endpoints.

A tipping point analysis will be performed based on implementing a delta-adjusted MI approach. The delta-adjusted imputation approach allows for missing data to be imputed under a MNAR assumption. Heuristically, the imputation strategy, adjusts/shifts the parameters of the MAR distribution based on the value of a numeric offset term, denoted by delta. The tipping point analysis will adjust the values of the parameters in the MAR distribution representing the mean change in EASI score from baseline to Week 16. The analysis will assess how robust the results of the main analysis are to varying departures from the MAR assumption within each treatment group. The range of the shift parameter for the treatment arms will be specified in the SAP along with the seed, the MAR imputation strategy, and the number of imputations.

Supplementary analysis
For the continuous endpoints related to the EASI score, the primary analysis will be repeated for all protocol-defined visit weeks.

11.3.8.2 Analysis of primary estimand for binary endpoints

Subjects receiving rescue treatment or who have permanently discontinued IMP due to lack of efficacy, or the occurrence of an AE related to worsening of AD, prior to the endpoint of interest, are defined as non-responders, reflecting an assumption that the occurrence of such intercurrent events indicates a failure of the randomized treatment.

Data observed after the permanent discontinuation of IMP for reasons besides lack of efficacy or the occurrence of an AE related to worsening of AD will be excluded from the analysis and treated as missing. Missing data and data treated as missing will be imputed using MI (100 iterations) under a MAR assumption within each treatment group. All subject-level data observed prior to the occurrence of an intercurrent event will be used to inform the imputation

models. Further details regarding the specification of the imputation models will be specified in the SAP.

The 100 complete datasets will be analyzed based on a logistic regression model, including treatment, baseline disease severity (vIGA-AD score at baseline), region (Japan, Other countries), prior use of biologics or systemic JAK inhibitors for AD (Yes/No) and the baseline value of the endpoint as a covariate. The logistic regression model will be used to estimate the risk, risk difference, and associated 95% CI based on the standardized estimator presented in Bartlett (80). For the analysis of the vIGA-AD responder endpoints, baseline disease severity will not be included as a covariate in the logistic regression model.

The pooled estimate of the risk difference, along with the associated 95% CIs and nominal p-values will be presented. Inference will be based on applying Rubin's rules to the estimates obtained from the analysis of the imputed data sets using the standardized estimator.

Sensitivity analysis
A 2-dimensional tipping point sensitivity analysis will be performed for the binary endpoints related to EASI, vIGA-AD, and ADSD Worst [redacted] score.

For each treatment comparison versus placebo, responder statuses that are either missing or treated as missing will be imputed for both arms across a range of response probabilities. The exact range, along with the number of imputations, imputation models, and the seeds will be specified in the SAP. The multiple imputed complete data sets for each point in the 2-dimensional tipping point analysis will be analyzed as specified for the primary analysis. For the cases where there is no variation in the imputed response statuses, the analysis will be conducted based on fitting the logistic regression model (as described earlier in this section) to a single complete data set. The p-values from the analysis of each point in the 2-dimensional tipping point analysis will be presented in a figure, along with any potentially identified tipping point (in this case a tipping line).

Supplementary analysis
For the binary endpoints related to EASI, vIGA-AD and ADSD Worst [redacted] score, the primary estimand will be analyzed for all protocol-defined visit weeks.

11.3.8.3 Analysis of primary estimand for time-to-event endpoint

Primary analysis
Let T represent the time from baseline to initiation of rescue treatment and T_{IE} represent the time from baseline to occurrence of permanent discontinuation of IMP or withdrawal from trial. The *while on treatment* estimand evaluates:

$$Pr(T < T_{IE} \wedge C_{admin})$$

where $T_{IE} \wedge C_{admin}$ is the minimum of T_{IE} and the end of the treatment period (administrative censoring time), corresponding to Week 16. Since interest lies in estimating the time to initiating rescue treatment, the occurrence of permanent discontinuation of IMP or withdrawal from trial can be accounted for through the formulation of a competing risks model.

The null hypothesis, $H_{0,i}$: $\lambda_{\text{LEO 138559, regimen i}}(t) = \lambda_{\text{placebo}}(t)$, $\forall\ t \in (0,16)$, where $\lambda(t)$ denotes the sub-distribution hazard rate associated with the time-to-event endpoint at time t (measured in weeks) and $i \in (1,2,3,4)$ denotes the LEO 138559 dose regimen, will be tested against the alternative, $H_{A,i}$: $\lambda_{\text{LEO 138559, dosage regimen i}}(t) \neq \lambda_{\text{placebo}}(t)$ based on Gray's test, stratified by baseline disease severity (baseline vIGA-AD score), region (Japan, Other countries), and prior use of biologics or systemic JAK inhibitors for AD (Yes/No).

To quantify the magnitude of the potential treatment effect, the estimated cumulative incidence functions for the competing risks model will be presented for the treatment groups, based on the Aalen-Johansen estimator, along with 95% CIs.

11.3.9 Supplementary estimand analysis

11.3.9.1 Analysis of hypothetical supplementary estimand for continuous endpoints

Primary analysis

Data collected after permanent discontinuation of IMP or after initiation of rescue treatment will be excluded from the analysis and "treated as missing". Missing data and data "treated as missing" will be split into two groups:

1. Data "treated as missing" due to discontinuation due to lack of efficacy, an AE related to worsening of AD, or rescue treatment.
2. Missing data or data "treated as missing" for other reasons than discontinuation due to lack of efficacy, an AE related to worsening of AD, or rescue treatment.

The first group will have their missing values imputed using an ANCOVA model adjusting for treatment, region, and time as a continuous covariate. Noise will be added to the predicted values from the imputation model. The imputation will be repeated 100 times. Further details regarding the imputation model, including choice of seed, will be specified in the SAP.

The second group will be imputed using MI (100 iterations) under a MAR assumption within each treatment group. All subject-level data observed prior to the occurrence of an intercurrent event will be used to inform the imputation models. Further details regarding the specification of the imputation models will be specified in the SAP.

The imputed datasets will be combined to create 100 complete datasets. For each of the 100 complete datasets, the response will be analyzed using an ANCOVA model adjusted for treatment, baseline disease severity (baseline vIGA-AD score), region (Japan, Other countries), and prior use of biologics or systemic JAK inhibitors for AD (Yes/No). The model will also be adjusted for the baseline value of the dependent variable.

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

11.3.9.2 Analysis of second supplementary estimand for continuous endpoints

Primary analysis
All observed data will be included in the analysis, including data observed after the occurrence of intercurrent events.

Missing data will be imputed using MI (100 iterations) under a MAR assumption within each treatment group. All observed data will be used to inform the imputation model. Further details regarding the specification of the imputation models will be detailed in the SAP.

For each of the 100 complete datasets, the response will be analyzed using an ANCOVA model adjusted for treatment, baseline disease severity (baseline vIGA-AD score), region (Japan, Other countries), and prior use of biologics or systemic JAK inhibitors for AD (Yes/No). The model will also be adjusted for the baseline value of the dependent variable.

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

11.3.9.3 Analysis of supplementary estimand for binary endpoints

Primary analysis
All observed data will be included in the analysis, including data observed after the occurrence of intercurrent events.

Missing data will be imputed using MI (100 iterations) under a MAR assumption within each treatment group. All observed data will be used to inform the imputation model. Further details regarding the specification of the imputation models will be detailed in the SAP.

For each of the 100 complete datasets, the response will be analyzed using a logistic regression model including treatment, baseline disease severity (vIGA-AD score at baseline), region (Japan, Other countries), prior use of biologics or systemic JAK inhibitors for AD (Yes/No) and the baseline value of the endpoint as a covariate. For the analysis of the vIGA-AD responder endpoints, baseline disease severity will not be included as a factor in the logistic regression model.

The pooled estimate of the estimated risk differences and standard errors based on the standardized estimator presented in Bartlett (80), along with the associated 95% CIs and nominal p-values will be presented. Inference will be based on applying Rubin's rules to the estimates and standard errors from the analyses of the imputed datasets.

11.3.9.4 Analysis of supplementary estimand for time to event endpoint

Primary analysis

Let T represent the time from baseline to the initiation of rescue treatment or permanent discontinuation of IMP, whichever occurs first. The *composite* estimand evaluates:

$$Pr(T < C_{admin})$$

where C_{admin} is the end of the treatment period (administrative censoring time), corresponding to Week 16.

The null hypothesis, $H_{0,i}$: $\lambda_{\text{LEO 138559, regimen i}}(t) = \lambda_{\text{placebo}}(t)$, $\forall\ t \in (0,16)$, where $\lambda(t)$ denotes the hazard rate associated with the time-to-event endpoint at time t (measured in weeks) and $i \in (1,2,3,4)$ denotes the LEO 138559 dose regimen, will be tested against the alternative, $H_{A,i}$: $\lambda_{\text{LEO 138559, dosage regimen i}}(t) \neq \lambda_{\text{placebo}}(t)$ based on the log-rank test, stratified by baseline disease severity (baseline vIGA-AD score), region (Japan, Other countries), and prior biologics or systemic JAK inhibitors for AD (Yes/No).

To quantify the magnitude of the potential treatment effect, the estimated cumulative incidence functions will be presented for the treatment groups, based on the Kaplan-Meier estimator, along with 95% CIs. Additionally, the difference in the estimated cumulative incidence functions at Week 16 between the LEO 138559 dose regimens and placebo will be presented along with 95% CIs.

11.3.10 Analysis of baseline subgroup estimands

The baseline subgroup estimands will be analyzed according to the primary analysis for the primary estimand for binary endpoints, specified in Section 11.3.8.2.

11.3.11 PRO analysis

Endpoints related to PROs will be analyzed as described in Section 11.3.7.

11.3.12 PD

For the following endpoints, explorative analyses will be performed for the total population as well as by baseline disease severity:

- Change in expression of biomarkers in serum from baseline to Week 2, Week 4, and to Week 16, respectively.
- Change in skin *Staphylococcus aureus* abundance and microbiome profile from baseline to Week 16.
- Change in skin lipid and molecular profile from baseline to Week 4, and to Week 16, respectively.
- Change in biomarker expression from baseline to Week 16 in lesional skin biopsies.

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.

11.3.13 Safety analysis

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

11.3.13.1 AEs

Coding of AEs

AEs will be coded during the course of the trial according to MedDRA. AEs defined by MedDRA PTs within primary SOC will be presented.

TEAEs

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 TEAEs. All AEs recorded during the course of the trial will be included in subject data listings.

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

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

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

Tabulations by SOC and PT 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.

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

AEs leading to withdrawal from trial or permanent discontinuation of IMP will be tabulated and listed. No narratives will be given.

Other events (medication error) will be listed. No narratives will be given.

11.3.13.2 Vital signs

The change in vital signs (resting BP, pulse, and body temperature) from baseline to each relevant visit will be summarized as mean, SD, median, minimum, and maximum values for each treatment group. Shift table for clinically significant abnormal vital signs will be presented.

11.3.13.3 ECG

Subjects with abnormal, clinically significant ECG will be listed. Furthermore, a shift table for ECG showing the change from baseline to end-of-treatment in clinical assessment (normal; abnormal, not clinically significant; abnormal, clinically significant) will be provided.

11.3.13.4 Clinical laboratory evaluation

The change in each of the laboratory parameters (except from hematology ratios) from baseline to each relevant visit will be summarized as mean, SD, median, minimum, and maximum values for each treatment group.

For liver and kidney parameters (ALP, ALT, AST, BIL, and eGFR) and white blood cells (neutrophils, lymphocytes, and eosinophils), guideline or literature defined thresholds will be used for producing shift tables and categorical threshold tables. The remaining laboratory parameters will be classified as ‘low’, ‘normal’, or ‘high’, depending on whether the value is below, within, or above the reference range and these categories will be used for producing shift tables.

If any subjects have concurrent elevations of alkaline phosphatase, ALT, AST, and bilirubin, per the guideline or literature defined thresholds, an individual profile plot of the subjects' alkaline phosphatase, ALT, AST, and bilirubin over the trial period will be provided.

11.3.13.5 ADA

For the endpoint on having a positive ADA response from baseline to Week 32, the ADA status (positive vs. negative) at each assessment time point will be summarized 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 summarized 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 summarized 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.

11.3.14 PK analysis

The following endpoint will be evaluated based on the PK analysis set:

- Serum concentration of LEO 138559 at Weeks 1, 2, 4, 8, 12, 16, 20, and 32.

LEO 138559 serum concentrations will be listed and summarized by treatment group and visit.

11.3.15 Interim analysis

No interim analysis is planned.

11.3.16 Timing of reporting trial results

The trial will be unblinded once all randomized 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 follow-up period.

A written plan (trial blinding plan) detailing the blinded/unblinded staff for the reporting of trial results based on the data lock point date of the last subject's Week 16 visit will be prepared before FSFV.

12 Supporting documentation and operational considerations

12.1 Appendix 1: Regulatory, ethical, and trial governance considerations

12.1.1 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 (61) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (81).
- Current version of applicable ICH GCP Guidelines (1).
- 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 fulfill its responsibilities (such as the trial protocol, protocol amendments, investigator's brochure, subject information sheet, and ICF(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 favorable opinion from relevant regulatory authorities and IRBs/IECs, as required, prior to implementation.

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

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the local IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Informing LEO Pharma immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard.
- Providing oversight of the conduct of the trial at the trial site and ensuring adherence to applicable national and international legislation.

Handling of serious breach

A serious breach is any deviation of the approved protocol version or the clinical trial regulation that is likely to affect the safety, rights of trial subjects and/or data reliability and robustness to a significant degree in a clinical trial.

The investigator and all site staff are responsible for reporting suspected serious breaches to LEO Pharma without undue delay and no later than 24 hours of obtaining knowledge.

Suspected serious breaches must be reported to the CRA.

If necessary for reporting the incident to the affected member state through the EU portal, LEO Pharma may request additional information from the reporter.

12.1.2 Financial disclosure

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

12.1.3 Informed consent process

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

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

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

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

Subject card

At screening, subjects will be provided with a card stating that they are participating in a clinical trial and which 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 system cannot be performed.

12.1.4 Recruitment strategy

The recruitment strategy and tools will be the below including, but not limited to:

Recruitment tools as approved by the regulatory authorities and IRB/IEC:

- Advertisement – Poster, flier, brochure
- HCP referral letter

Local, site-initiated advertisement will be subject to the sponsor's review and approval prior to submission to their local/central IRB/IEC.

12.1.5 Data protection

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. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

Trial subjects must be informed that their medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by LEO Pharma, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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

Processing of personal data

This protocol specifies the personal data on trial subjects (e.g. race, ethnicity, age, sex, health condition, medical history, test results, etc.) which shall be collected as part of the clinical trial and processed during and after trial completion.

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

Processing of personal data on behalf of LEO Pharma requires a written agreement between LEO Pharma and the relevant party which covers collection, processing, and transfer of personal data in the clinical trial 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 must be informed of the collection, processing, and transfer of their personal data to EU and non-EU countries for the purpose of conducting the clinical trial, research and development of new or existing products/services, improving existing products/services, applying for marketing authorizations for products/services, marketing of products/services, and other related activities.

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

12.1.6 Committee structure

Not applicable.

12.1.7 Dissemination of clinical trial data

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

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

Results of this clinical trial will be posted in accordance with applicable laws and regulations as well as LEO Pharma’s commitment to transparency which can be found on LEO Pharma’s website.

12.1.8 Data quality assurance

Data will be collected by means of EDC unless transmitted electronically to LEO Pharma or designee (e.g. laboratory data). The investigator or staff authorized by the investigator will enter subject data into an eCRF. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

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

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The monitoring will be performed in a systematic, prioritized, risk-based approach, and as a combination of on-site, remote, and centralized monitoring.

LEO Pharma or designee is responsible for the data management of this trial including quality checking of the data.

LEO Pharma assumes accountability for actions delegated to other individuals (e.g. CROs).

Records and documents, including signed ICF, pertaining to the conduct of this trial must be retained by the investigator for 25 years after trial completion unless otherwise required by local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of LEO Pharma. No records may be transferred to another location or party without the written approval of LEO Pharma.

All data generated by the site personnel will be captured electronically at each trial site using eCRFs. Once the eCRF clinical data have been submitted to the central server, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible CRA or data manager will raise a query in the electronic data capture application. The appropriate staff at the trial site will answer queries sent to the investigator. The name of the staff member responding to the query, and

time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the data manager or CRA will freeze the eCRF page.

Site personnel will receive training on the EDC system/eCRF. The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be described in the CRF completion guidelines.

12.1.9 Source documents

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. Safety evaluations must be signed and dated by a physician. Clinical assessments must be signed and dated by the investigator.

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.
- Randomization 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.

12.1.10 Trial and trial site start and closure

First act of recruitment

The trial start date is the date on which the clinical trial will be open for recruitment of subjects.

The first act of recruitment is the first subject first visit.

Trial/site termination

LEO Pharma or designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of LEO Pharma. Trial sites will be closed upon trial

completion. 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.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, LEO Pharma procedures, or GCP guidelines.
- Inadequate recruitment (evaluated after a reasonable amount of time) of subjects by the investigator.
- Total number of subjects included earlier than expected (irrespective of the specific site's planned inclusion number).

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

12.1.11 Publication policy

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

A multi-site publication will be submitted for publication within 12 months after the clinical trial has been completed or terminated at all trial sites and all data have been received, defined as final database lock of the clinical trial. After such multi-site publication is made public, or if no multi-site publication has been submitted with the above-described deadline, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements:

Prior to submission for publication or presenting a manuscript relating to the clinical trial, the investigator shall provide to LEO Pharma a copy of all such manuscripts and/or presentations. LEO Pharma shall have rights to review and comment. The investigator shall consider

comments provided by LEO Pharma but is not required to modify the manuscript and/or presentation based on such comments, provided, however, that the investigator upon the request of LEO Pharma remove any confidential information (other than results generated by the investigator) prior to submitting or presenting the manuscripts. The investigator shall, upon the request of LEO Pharma withhold the publication or presentation to allow LEO Pharma to protect its inventions and other intellectual property rights described in any such manuscripts.

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

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

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

LEO Pharma complies with GPP3 standards and the recommendations from the International Committee of Medical Journal Editors. LEO Pharma complies with the positions of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), and the joint position statement by the American Medical Writers Association (AMWA), the European Medical Writers Association (EMWA), and the International Society for Medical Publication Professionals (ISMPP) on disclosure of information about clinical trials, trial results, and authorship. LEO Pharma also follows the CONSORT reporting guidelines (63).

12.1.12 Insurance

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

12.2 Appendix 2: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

12.2.1 AE definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (82).

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavorable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures*.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 8.4.5.2).

12.2.2 SAE definition

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening – at risk of death at the time of the SAE (not an event that hypothetically might have caused death if more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization*.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is a medically important condition. Events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, and convulsions that do not result in hospitalization, development of drug dependency, or drug abuse.

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

*Hospitalization for procedures or treatments planned prior to the subject consented to trial participation does not constitute an AE and should therefore not be reported as an AE or SAE.
*Hospitalization for elective treatment of a pre-existing condition which did not worsen from the subject consented to trial participation is not considered an AE and should therefore not be reported as an AE or SAE, even if not planned before consent to trial participation.
*Hospitalization for routine scheduled treatment or monitoring of the studied indication not associated with any aggravation of the condition does not constitute an AE and should therefore not be reported as an AE or SAE.
*Hospitalization for administrative, trial-related, or social purpose does not constitute an AE and should therefore not be reported as an AE or SAE.
*Complications that occur during hospitalization are (S)AEs. If a complication prolongs hospitalization, the event is an SAE.
*When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

12.2.3 Definition of AESIs

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

AESIs are described in Section 10.7.1.

12.2.4 Recording and follow-up of AEs

AE recording

When an AE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.

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

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

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s) (including the trial disease), compared to screening, must be reported as an AE.

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

The duration of the AE must be reported by the start date and stop date of the event unless the event is ongoing. If the event is ongoing, it will be marked as ongoing. In addition, it will be recorded whether the AE started on the same day as IMP was administered and if so, whether before or after IMP dosing.

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

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).

For subjects participating in the qualitative interview, AEs reported during the interview may be reported retrospectively.

Any potential AE reported by the subjects during the qualitative interview must be collected by the interviewer on the Potential Adverse Event Collection Form. The interviewer must forward the completed form to the investigator within 24 hours of the interview. The investigator must evaluate if the potential AEs are indeed to be considered as AEs and whether they were already recorded in the eCRF and date and sign their evaluation within 24 hours of receipt of the form. Investigator should confirm review of the form directly in the secure IT portal within those 24 hours. If the confirmed AEs were not recorded in the eCRF, or if the investigator is in doubt, they must record the AEs in the eCRF. If considered relevant, the investigator should follow up on the AEs with the subject at the safety follow-up visit. If a potential AE qualifies as an SAE, the SAE must be reported within 24 hours of receipt by the site/investigator as described in Section 12.2.5.

Assessment of severity

The *severity* of the AE should be described in terms of mild, moderate, or severe according to the investigator's clinical judgement. If the AE worsens in severity, the new severity, including date of worsening, should be recorded. However, if an AE with onset prior to IMP initiation worsens after IMP administration, a new AE should be recorded.

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.

Assessment of causality

The investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship.

A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.

The investigator will also consult the LEO 138559 investigator's brochure in their assessment.

For each AE, the investigator must document in the medical notes that he/she has reviewed the AE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial SAE form. However, it is very important that the investigator always assesses causality for every event before the initial recording of the SAE data.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The following decision choices will be used by the investigator to describe the causality assessment:

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.

Assessment of outcome

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

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

Follow-up of AE

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 possibly or probably related to the IMP for 2 weeks or until the final outcome is determined, whichever comes first. Non-serious AEs classified as not related to the IMP do not need to be followed up for the final outcome.

All SAEs must be followed up until a final outcome has been established, that is, the follow-up may continue beyond the end of the clinical trial. For SAEs which have stabilized and from which the subject cannot be expected to recover during the trial or the safety follow-up periods, e.g. chronic or stabilized conditions, the final outcome should be reported as 'recovering/resolving' or 'not recovered/not resolved' at the investigator's discretion. In addition, a statement detailing why the subject cannot be expected to recover during the trial, e.g. that the SAE has stabilized or is chronic, should be added to the narrative description of the SAE on the SAE form.

The investigator is obligated to arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by LEO Pharma to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the trial or during a recognized follow-up period, the investigator will provide LEO Pharma with a copy of any post-mortem findings including histopathology, if available.

New or updated information will be recorded in the originally completed form.

The investigator will submit any updated SAE data to LEO Pharma within 24 hours of receipt of the information.

12.2.5 Reporting of SAEs

Investigator reporting responsibilities

Any SAE must be reported to LEO Pharma on the (paper) SAE form immediately, without undue delay and no later than 24 hours of obtaining knowledge. This report should contain amongst others an assessment of available information on seriousness, severity, causal relationship to the IMP or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event. For more details regarding reporting of any SAE, please see the guidance text on the SAE form.

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

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

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

Global Safety at LEO Pharma

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

Fax number: +45 6910 2468

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

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

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

SAEs occurring after the completion of the clinical trial should not be routinely sought or recorded. If the investigator becomes aware of an SAE with a suspected causal relationship to

the IMP that occurs after the end of the clinical trial in a subject treated by him or her, the investigator shall, without undue delay, report the SAE to Global Safety at LEO Pharma (see contact details above).

LEO Pharma reporting responsibilities

Global Safety at LEO Pharma is responsible for assessing whether an SAE is expected. The relevant reference safety information document for this clinical trial is the investigator's brochure Section 7.3, edition 5.0 and subsequent updates (49).

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 (1), and which are unexpected (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 (83, 84) and which are unexpected (serious and unexpected suspected adverse reactions [IND safety report]) are subject to expedited reporting to regulatory authorities, IRB(s). Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

12.2.6 Narratives

In the CTR, narratives will be provided for the following:

- SAEs.
- Deaths.
- AESIs

12.3 Appendix 3: Hanifin and Rajka (1980) diagnostic criteria for AD

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

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

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

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

12.4 Appendix 4: Guidance for anaphylaxis diagnosis

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

Clinical criteria for diagnosing anaphylaxis

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

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

AND AT LEAST ONE OF THE FOLLOWING:

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

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   - Involvement of the skin-mucosal tissue (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula).
   - Respiratory compromise (e.g. 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.

12.5 Appendix 5: Country-specific requirements

12.5.1 Specific requirements for all EU countries

This section describes requirements and procedures that are specific for all EU countries i.e. CZ, DE, ES, FR, HU, PL and RO.

The schedule of trial activities specific for EU countries is presented in Section 12.5.1.1 (Panel 18). The list of eligibility criteria specific for EU countries is presented in Section 12.5.1.2.

For each section, the text from the protocol is presented in normal font. The country-specific requirements or procedures are presented below in **bold** and deleted text has a line through it.

Section 1.3 **Schedule of activities**

Panel 18: Schedule of trial activities for EU countries

Assessments of vital signs should also be performed at Week 6 (Visit 8), Week 10 (Visit 10), and Week 14 (Visit 12).

Panel 18: Schedule of trial activities for EU countries, footnote o) related to vital signs will be: **Vital signs must be assessed prior to IMP administration. In addition,** at Weeks 0, 1, 2, 3, and 4, subjects will be monitored after IMP administration for potential immediate drug reactions for a minimum of 2 hours with vital signs taken immediately (within 5 minutes) after last IMP administration as well as after 30 minutes (± 5 minutes), after 1 hour (± 5 minutes), and after 2 hours (± 5 minutes), or until stable, whichever is later. **From Week 5 onwards, subjects will be monitored after IMP administration for potential immediate drug reactions for a minimum of 20 minutes with vital signs assessed within 5 minutes after last IMP administration as well as after 20 minutes (± 5 minutes), or until stable, whichever is later.**

Panel 18: Schedule of trial activities for EU countries

Assessments of hepatitis B and hepatitis C should also be performed at Week 12 (Visit 11), and Week 24 (Visit 15).

Panel 18: Schedule of trial activities for EU countries, an additional footnote p) related to hepatitis B, hepatitis C and HIV will be added: **For subjects who at screening have a negative HBV-DNA reflex test (i.e. HBV-DNA is not detected), and negative HBsAg, negative anti-HBc, positive anti-HBs and without documentation of prior HBV**

vaccination or negative HBsAg and positive anti-HBc, repeat HBV-DNA will be done at Weeks 12 and 24. For subjects who at screening have positive anti-HCV but negative HCV-RNA (i.e. HCV-RNA is not detected), repeat HCV-RNA will be done at Weeks 12 and 24.

Panel 18: Schedule of trial activities for EU countries

Assessments of chemistry and hematology (central laboratory) should also be performed at Week 1 (Visit 4), Week 2 (Visit 5), and Week 3 (Visit 6).

Section 2.4 **Ethical considerations**

In addition, at Weeks 0, 1, 2, 3, and 4, subjects will be monitored for a period of 2 hours to detect potential immediate drug reactions, and from Week 5 onwards, subjects will be monitored for a period of 20 minutes.

Section 5.3 **Exclusion criteria**

Exclusion criterion #8

Positive HBsAg or positive anti-HCV AND positive HCV-RNA at screening.

- Subjects with a negative HBsAg and a positive anti-HBc or anti-HBs at screening will have reflex testing for HBV-DNA. **Subjects who have a positive HBV-DNA test (i.e. HBV-DNA is detected) will be excluded.**
- **For subjects who at screening have a negative HBV-DNA reflex test (i.e. HBV-DNA is not detected), and**

  Negative HBsAg, negative anti-HBc, positive anti-HBs and without documentation of prior HBV vaccination

  or

  Negative HBsAg and positive anti-HBc

  repeat HBV-DNA testing must be done at Weeks 12 and 24. If HBV-DNA is positive (i.e. HBV-DNA is detected) at Week 12, subjects must permanently discontinue IMP.
- **Subjects who at screening have a negative HBV-DNA reflex test (i.e. HBV-DNA is not detected), negative HBsAg, negative anti-HBc, positive anti-HBs and provide documentation of prior HBV vaccination will not require regular monitoring by HBV-DNA repeat testing in the trial.**
- **For subjects who at screening have positive anti-HCV but negative HCV-RNA (i.e. HCV-RNA is not detected), repeat HCV-RNA will be done at Weeks 12 and 24. If HCV-RNA is positive (i.e. HCV-RNA is detected) at Week 12, subjects must permanently discontinue IMP.**

Exclusion criterion #14

Any disorder* at screening and/or baseline, which is not stable in the opinion of the investigator, and could:
-Affect the safety of the subject throughout the trial.
- Influence the results of the trial.
- Impede the subject's ability to complete the trial.

[redacted]

Exclusion criterion #15

Any significant abnormal finding* at screening and/or baseline which may in the opinion of the investigator:
- Put the subject at risk because of their participation in the trial.
- Influence the results of the trial.
- Influence the subject's ability to complete the trial.

*The abnormal finding must be clinically significant and observed during the screening period. Examples include **but are not limited to** abnormal findings in physical examination, vital signs, ECG, hematology **(e.g. hemoglobin <100 g/L, neutrophils <1.5 x 10^9/L, thrombocytes <75 x 10^9/L)**, biochemistry **(e.g. serum creatinine >1.5 times the ULN, bilirubin >1.5 times the ULN; subjects with a history of Gilbert's syndrome are eligible for this trial provided direct bilirubin is < the ULN)**, or urinalysis.

Exclusion criterion #30

Subjects who are legally institutionalized **or legally protected (e.g. those under guardianship, curatorship, safeguard of justice) or other subjects incapable of giving informed consent according to the law of his/her residing country**.

Section 6.2 **Administration of IMP**

At Weeks 0, 1, 2, 3, and 4, subjects will be monitored for potential immediate drug reactions for a minimum of 2 hours after IMP administration. Vital signs will be taken immediately (within 5 minutes) after last IMP administration, as well as after 30 minutes (± 5 minutes), after 1 hour (± 5 minutes), and after 2 hours (± 5 minutes), or until stable, whichever is later. **From Week 5 onwards, subjects will be monitored after IMP administration for potential immediate drug reactions for a minimum of 20 minutes with vital signs assessed within 5 minutes after last IMP administration as well as after 20 minutes (± 5 minutes), or until stable, whichever is later.** Vital signs will be documented in the eCRF.

Section 7.2.1 **Reasons for permanent discontinuation of IMP**

• Positive HBV-DNA test (i.e. HBV-DNA is detected) at Week 12 (see exclusion criterion no. 8).
• Positive HCV-RNA test (i.e. HCV-RNA is detected) at Week 12 (see exclusion criterion no. 8).

Section 8.4.1 **Vital signs**

At Weeks 0, 1, 2, 3, and 4, subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken immediately (within 5 minutes) after last IMP administration, after 30 minutes (± 5 minutes), after 1 hour ± 5 minutes), and after 2 hours ± 5 minutes), or until stable, whichever is later. **From Week 5 onwards, subjects will be monitored after IMP administration for potential immediate drug reactions for a minimum of 20 minutes with vital signs assessed within 5 minutes after last IMP administration as well as after 20 minutes ± 5 minutes), or until stable, whichever is later.**

Section 8.4.5.2 **Investigator evaluation of laboratory samples**

If the urine pregnancy test is positive but not confirmed by ~~the~~ **repeated** serum pregnancy test, the subject may continue IMP treatment, but the LEO medical expert should be consulted.

12.5.1.1 Schedule of activities specific for EU countries

Panel 18: Schedule of trial activities for EU countries

	Screening[a]		Treatment period											Follow-up				Early term, if app.[b],[c],[d]	Uns. visit[e]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EoT[b]**	**14**	**15**	**16**	**17[b],[c]**			
Week	**-4**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16[b]**	**20**	**24**	**28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**			
Visit window (days)[f]	**NA**	**-3**	**NA**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Administrative and baseline procedures																				
Informed consent[g]	X																			App 1 (12.1.3)
Subject eligibility	X		X																	5.2 and 5.3
Demographics	X																			8.2.1
Medical history	X																			8.2.2
Body measurement (height)	X																			8.2.3
Serum pregnancy test[h]	X																			8.2.5
C-SSRS	X																			8.2.4

	Screening[a]		Treatment period											Follow-up				Early term, if app.[b],[c],[d]	Uns. visit[e]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EoT[b]**	**14**	**15**	**16**	**17[b],[c]**			
Week	**-4**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16[b]**	**20**	**24**	**28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**			
Visit window (days)[f]	**NA**	**-3**	**NA**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Treatments and randomization																				
Randomization			X[k]																	6.3
IMP administration[o] and compliance			X	X	X	X	X	X	X	X	X	X							(X)	6.2 and 6.8.3
Background treatment (moisturizer)[i]	<==========																==========>			6.4
Concomitant medication[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	6.6
Concurrent procedures[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	6.6
Assessments of efficacy: Investigator assessments																				
EASI	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	8.3.1
SCORAD	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	8.3.2
vIGA-AD	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	8.3.3
Assessments of efficacy: Subject assessments																				
eDiary hand-out/training	X																			

	Screening[a)]		Treatment period											Follow-up				Early term, if app.[b),c),d)]	Uns. visit[e)]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EoT[b)]**	**14**	**15**	**16**	**17[b),c)]**			
Week	**-4**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16[b)]**	**20**	**24**	**28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**			
Visit window (days)[f)]	**NA**	**-3**	**NA**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Return of eDiary																	X			
eDiary completion[l)]		<==========																===>		8.3.5.1
DLQI			X	X			X		X		X	X	X					(X)	(X)	8.3.5.6
POEM			X	X			X		X		X	X	X					(X)	(X)	8.3.5.7
EQ-5D-5L			X				X		X		X	X	X					(X)	(X)	8.3.5.8
WPAI-SHP			X										X					(X)	(X)	8.3.5.9
HADS			X										X					(X)	(X)	8.3.5.10
PGI-S[m)]			X				X		X		X	X	X					(X)	(X)	8.3.5.11
PGI-C[n)]							X		X		X	X	X					(X)	(X)	8.3.5.12
Assessments of safety																				
Vital signs[o)]	X		X	X	X	X	X	X	X	X	X	X	X	X			X	(X)	(X)	8.4.1
Physical examination	X		X										X					(X)	(X)	8.4.2
Body measurement (weight)	X		X										X					(X)	(X)	8.4.3
ECG	X		X				X		X				X				X	(X)	(X)	8.4.4
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	10

	Screening[a]		Treatment period											Follow-up				Early term, if app.[b],[c],[d]	Uns. visit[e]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EoT[b]**	**14**	**15**	**16**	**17[b],[c]**			
Week	**-4**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16[b]**	**20**	**24**	**28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**			
Visit window (days)[f]	**NA**	**-3**	**NA**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Laboratory tests																				
Hepatitis B and C, HIV	X										X[p]				X[p]					8.2.5
Tuberculosis test	X																			8.2.5
Chemistry and hematology (central laboratory)	X		X	X	X	X	X		X		X		X	X			X	(X)	(X)	8.4.5
IgE	X		X				X		X		X		X	X			X	(X)	(X)	8.4.5
Urinalysis (urine dipstick)	X		X				X		X		X		X	X			X	(X)	(X)	8.4.5
Urine pregnancy test			X				X		X		X		X	X	X	X	X	(X)	(X)	8.4.5
ADA			X		X								X	X			X	(X)	(X)	8.4.6
Other assessments: Pharmacokinetics																				
Blood sample (LEO 138559 serum concentration)[q]				X	X		X		X		X		X	X			X	(X)	(X)	8.5

	Screening[a)]		Treatment period											Follow-up				Early term, if app.[b),c),d)]	Uns. visit[e)]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EoT[b)]**	**14**	**15**	**16**	**17[b),c)]**			
Week	**-4**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16[b)]**	**20**	**24**	**28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**			
Visit window (days)[f)]	**NA**	**-3**	**NA**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Other assessments: Pharmacodynamics																				
Blood sample (biomarkers)			X		X		X		X				X					(X)	(X)	8.6
Skin swabs (*Staphylococcus aureus* abundance) and microbiome profiling			X										X					(X)	(X)	8.6
Skin tape strips (molecular profile)[r)]			X				X						X					(X)	(X)	8.6
Skin biopsies (biomarker expression)[s)]			X										X							8.6

	Screening[a)]		Treatment period											Follow-up				Early term, if app.[b),c),d)]	Uns. visit[e)]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ EoT[b)]**	**14**	**15**	**16**	**17[b),c)]**			
Week	**-4**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16[b)]**	**20**	**24**	**28**	**32**			
Day	**-28**	**-7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**			
Visit window (days)[f)]	**NA**	**-3**	**NA**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Other assessments: Photography																				
Photography[t)]			X				X		X		X		X					(X)	(X)	8.7.1
Other assessments: Qualitative interviews in DE and PL[u)]																				
Scheduling interview										X										8.7.2
Clinigma to conduct trial interviews												X								8.7.2
End of treatment/trial																				
End of treatment[v)]													X					X	(X)	8.8
End of trial[w)]																	X	X[x)]	(X)	8.8

a) The screening period has a maximum duration of 4 weeks, with 2 planned visits. Visit 2 can be conducted by phone or on site.

b) Subjects who permanently discontinue IMP for any reason will be asked to attend an early termination visit as soon as possible after discontinuation of IMP. Subjects should be encouraged to attend all trial visits and be assessed for safety and efficacy according to the schedule of assessments. For subjects who no longer wish to attend all trial visits, the following visits should be prioritized: The primary endpoint visit (i.e. the Week 16 visit) and a final follow-up visit 18 weeks after last administration of IMP (with assessments identical to those to be done at the regular Week 32 visit).

c) Subjects who withdraw from the trial prior to Week 16 will be asked to attend an early termination visit as soon as possible after withdrawal (with assessments identical to those to be done at the regular Week 32 visit).

d) Some assessments to be performed at early termination visits will be at the discretion of the investigator. These are marked with an (X) in the table.

e) Assessments to be performed at unscheduled visits will be at the discretion of the investigator (marked with an (X) in the table).

f) 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 randomization/baseline.

g) The ICF must be signed prior to performing any protocol-related procedures, including, but not limited to, screening evaluations and washout of prohibited medications.

h) Only for women of childbearing potential (as defined in inclusion criterion no. 10).

i) Subjects should continue using their current daily skin care moisturizing routine from screening throughout the trial (until Week 32), if approved by the investigator, who will otherwise make an alternative suggestion.

j) Any medication, vaccine, or procedure received/performed from 3 months (12 months for medications related to AD) prior to screening through end of trial must be recorded.

k) In order to ensure a sufficient number of subjects naive for biologics and systemic JAK inhibitors used for their AD, there will be a capping at 50% of subjects who received prior treatment with such therapies.

l) Nocturnal [redacted], Difficulty [redacted], and Frequency of [redacted] During the Night (to be completed in the morning), and ADSD (to be completed in the evening) will be initiated at least 7 days prior to baseline (Day 1) and will be completed in the eDiary daily. After Week 16, only ADSD will be completed. Subjects who discontinue IMP, but remain in the trial, will continue completing the eDiary until the Week 16 visit.

m) PGI-S includes: [redacted], ADSD, Nocturnal [redacted], Difficulty [redacted], and Frequency of [redacted] During the Night.

n) PGI-C includes: [redacted], ADSD, Nocturnal [redacted], Difficulty [redacted], and Frequency of [redacted] During the Night.

o) Vital signs must be assessed prior to IMP administration. In addition, at Weeks 0, 1, 2, 3, and 4, subjects will be monitored after IMP administration for potential immediate drug reactions for a minimum of 2 hours with vital signs taken immediately (within 5 minutes) after last IMP administration as well as after 30 minutes (± 5 minutes), after 1 hour (± 5 minutes), and after 2 hours (± 5 minutes), or until stable, whichever is later. From Week 5 onwards, subjects will be monitored after IMP administration for potential immediate drug reactions for a minimum of 20 minutes with vital signs assessed within 5 minutes after last IMP administration as well as after 20 minutes (± 5 minutes), or until stable, whichever is later.

p) For subjects who at screening have a negative HBV-DNA reflex test (i.e. HBV-DNA is not detected), and negative HBsAg, negative anti-HBc, positive anti-HBs and without documentation of prior HBV vaccination or negative HBsAg and positive anti-HBc, repeat HBV-DNA will be done at Weeks 12 and 24. For subjects who at screening have positive anti-HCV but negative HCV-RNA (i.e. HCV-RNA is not detected), repeat HCV-RNA will be done at Weeks 12 and 24.

q) Samples to be collected pre-dose.

r) Skin tape strips will be collected at selected trial sites.

s) Skin biopsies will be collected at selected trial sites. It is voluntary for subjects at these sites to have skin biopsies collected, and if done, they will need to have provided informed consent to this component. Paired lesional and non-lesional biopsies will be collected at baseline. At the post-baseline visit, 1 biopsy will be collected from the original lesion; no skin biopsy will be collected from non-lesional skin at the post-baseline visit.

t) Photography will be performed at selected trial sites. It is voluntary for subjects at these sites to have photographs taken, and if done, they will need to have provided informed consent to this component.

u) Interviews will be conducted at selected trial sites. The interview will be scheduled to occur as soon as possible and within 14 days after Week 14 (Visit 12).

v) An end-of-treatment form must be completed once in the eCRF for all subjects exposed to IMP either at Week 16 or early termination.

w) An end-of-trial form must be completed in the eCRF for all subjects randomized and/or exposed to IMP.

x) Only applicable to subjects who withdraw from the trial prior to Week 16.

Abbreviations: AD = atopic dermatitis; ADA = anti-drug antibodies; ADSD = Atopic Dermatitis Symptom Diary; AE = adverse event; anti-HCV = hepatitis C virus antibody; app = applicable; C-SSRS = Columbia-Suicide Severity Rating Scale; DE = Germany; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eCRF = electronic case report form; eDiary = electronic diary; EoT = end-of-treatment; EQ-5D-5L = EuroQoL 5-Dimension Health Questionnaire 5 Level; HADS = Hospital Anxiety and Depression Scale; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; ICF = informed consent form; IgE = immunoglobulin E; IMP = investigational medicinal product; JAK = janus kinase; LLQ = lower level of quantification; NA = not applicable; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PL = Poland; POEM = Patient-Oriented Eczema Measure; RNA = ribonucleic acid; SCORAD = SCORing Atopic Dermatitis; term = termination; Uns = unscheduled; vIGA-AD = validated Investigator's Global Assessment for atopic dermatitis; WPAI-SHP = Work Productivity and Activity Impairment: Specific Health Problem.

12.5.1.2 Eligibility criteria specific for EU countries

INCLUSION CRITERIA

Subjects are eligible to be included in the trial only if all of the following criteria apply:

Informed consent

1. Signed and dated informed consent as described in Appendix 1 (Section 12.1.3) has been obtained prior to any protocol-related procedures.

Age

2. 18–75 years old (both included) at screening (Visit 1).

Compliance

3. Willingness to comply with the clinical trial protocol.

Type of subject and disease characteristics

4. At screening, diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD ((62) and Appendix 3 [Section 12.3]).
   - History of AD for ≥1 year.
5. Subjects who have a recent history (within 12 months before screening) with documented inadequate response to treatment with TCS (±TCI as appropriate) or for whom these topical AD treatments are medically inadvisable (e.g. due to important side effects or safety risks*).
   - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to higher potency (EU class II-IV, JP ≥ Medium, US class I-V) (±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 1 year are considered as inadequate responders to TCS 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.
6. EASI score ≥12 at screening and ≥16 at baseline.
7. vIGA-AD score ≥3 at screening and baseline.
8. BSA of AD involvement ≥10% at screening and baseline.
9. ADSD Worst [redacted] score (weekly average) ≥4 at baseline. The baseline weekly average will be calculated from daily assessments of [redacted] severity during the 7 days immediately preceding the baseline visit (Day -7 to Day -1). A minimum of 4 [redacted] scores out of the 7 days is required to calculate the baseline average score.

Contraceptive/barrier requirements

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

    * A woman of childbearing potential is defined as a female subject aged ≥12 years *or* a younger girl who, at the discretion of the investigator, is deemed to be of reproductive potential. A woman is defined as not being of childbearing potential if she is postmenopausal (at least 12 months with no menses prior to screening without an alternative medical cause), 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, IUD, 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 vasectomized partner (given that the subject is monogamous).

EXCLUSION CRITERIA

Subjects are excluded from the trial if any of the following criteria apply:

Medical conditions

1. Major* surgery within 8 weeks prior to screening, or planned inpatient surgery or hospitalization during the trial period (*at the discretion of the investigator).
2. Active dermatologic condition that could confound the diagnosis of AD or interfere with assessment of the treatment (e.g. scabies, contact dermatitis, rosacea, urticaria, or psoriasis).
3. History of cancer, with the following exceptions:
   - Subjects who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to screening.
   - Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to screening.
4. History of or current immunodeficiency syndrome.
5. History of anaphylaxis following any biologic therapy.
6. History of clinically significant infection within 4 weeks prior to baseline which, in the opinion of the investigator, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial. Clinically significant infections are defined as:
   - a systemic infection.
   - a serious skin infection requiring parenteral (IV or intramuscular) antibiotics, antiviral, or antifungal medication.

NOTE: Subject may be rescreened (once) after infection resolves. However, rescreening will require approval by the sponsor's medical expert (see Section 5.4).

7. Non-serious skin infection within 7 days prior to baseline. *NOTE: Subject may be rescreened (once) after infection resolves. However, rescreening will require approval by the sponsor's medical expert (see Section 5.4).*
8. Positive HBsAg or positive anti-HCV AND positive HCV-RNA at screening.
   - Subjects with a negative HBsAg and a positive anti-HBc or anti-HBs at screening will have reflex testing for HBV-DNA. Subjects who have a positive HBV-DNA test (i.e. HBV-DNA is detected) will be excluded.
   - For subjects who at screening have a negative HBV-DNA reflex test (i.e. HBV-DNA is not detected), and

     Negative HBsAg, negative anti-HBc, positive anti-HBs and without documentation of prior HBV vaccination

     or

     Negative HBsAg and positive anti-HBc

     repeat HBV-DNA testing must be done at Weeks 12 and 24. If HBV-DNA is positive (i.e. HBV-DNA is detected) at Week 12, subjects must permanently discontinue IMP.
   - Subjects who at screening have a negative HBV-DNA reflex test (i.e. HBV-DNA is not detected), negative HBsAg, negative anti-HBc, positive anti-HBs and provide documentation of prior HBV vaccination will not require regular monitoring by HBV-DNA repeat testing in the trial.
   - For subjects who at screening have positive anti-HCV but negative HCV-RNA (i.e. HCV-RNA is not detected), repeat HCV-RNA will be done at Weeks 12 and 24. If HCV-RNA is positive (i.e. HCV-RNA is detected) at Week 12, subjects must permanently discontinue IMP.
9. History of HIV infection or positive HIV serology at screening.
10. Evidence of active or latent tuberculosis according to local standard of care for patients requiring initiation of a biologic treatment.
    - A tuberculosis test can be performed at the central or local laboratory. Subjects with a positive or indeterminate test at screening will be excluded. *NOTE: Subject may be retested (once) if the initial test was indeterminate.*
11. ALT or AST level ≥2.0 times the ULN at screening.
12. Uncontrolled/untreated clinically significant depression or history of attempted suicide or is at significant risk of suicide (either in the opinion of the investigator or defined as a "yes" to suicidal ideation questions no. 4 or 5 or answering "yes" to suicidal behavior on the C-SSRS Screening version).
13. Known or suspected hypersensitivity to any component(s) of the IMP.
14. Any disorder* at screening and/or baseline, which is not stable in the opinion of the investigator, and could:
    - Affect the safety of the subject throughout the trial.
    - Influence the results of the trial.
    - Impede the subject's ability to complete the trial.

[redacted]

15. Any significant abnormal finding* at screening and/or baseline which may in the opinion of the investigator:
    - Put the subject at risk because of their participation in the trial.
    - Influence the results of the trial.
    - Influence the subject's ability to complete the trial.

    *The abnormal finding must be clinically significant and observed during the screening period. Examples include but are not limited to abnormal findings in physical examination, vital signs, ECG, hematology (e.g. hemoglobin <100 g/L, neutrophils <1.5 x 10^9/L, thrombocytes <75 x 10^9/L), biochemistry (e.g. serum creatinine >1.5 times the ULN, bilirubin >1.5 times the ULN; subjects with a history of Gilbert's syndrome are eligible for this trial provided direct bilirubin is < the ULN), or urinalysis.
16. Current or recent chronic alcohol or drug abuse, or any other condition associated with poor compliance as judged by the investigator.
17. Women who are pregnant or breastfeeding.

Prior/concomitant therapy

18. Previous treatment with LEO 138559.
19. Previous exposure to fezakinumab (anti-IL-22 Ab).
20. Systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporine, azathioprine), immunomodulating drugs, retinoids (e.g. alitretinoin), corticosteroids (steroid eyedrops and inhaled or intranasal steroids are allowed), or JAK inhibitors within 28 days or 5 half-lives prior to baseline, whichever is longer.
21. Use of tanning beds or phototherapy (NBUVB, UVB, UVA1, PUVA), within 4 weeks prior to baseline.
22. Receipt of blood products within 28 days prior to screening.
23. Treatment with:
    - Any marketed or investigational biologic agents within 3 months or 5 half-lives, whichever is longer, prior to baseline.
    - Any cell-depleting agents including but not limited to rituximab: within 6 months prior to baseline, or until lymphocyte count returns to normal, whichever is longer.
24. Treatment with TCS, TCI, topical PDE-4 inhibitors, topical JAK inhibitors, or other medicated topical treatments within 7 days prior to baseline. *NOTE: Subject may be rescreened (once) if failed for this criterion. However, rescreening will require approval by the sponsor's medical expert (see Section 5.4).*
25. Receipt of live attenuated vaccines 30 days prior to baseline or longer if recommended so by local guidelines.

26. 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 randomization, whichever is longer.

Prior/concurrent clinical trial experience

27. Current participation in any other interventional clinical trial.
28. Previously randomized in this clinical trial.

Other exclusion criteria

29. 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.
30. Subjects who are legally institutionalized or legally protected (e.g. those under guardianship, curatorship, safeguard of justice) or other subjects incapable of giving informed consent according to the law of his/her residing country.

12.5.2 Specific requirements for Czech Republic

This section describes requirements and procedures that are specific only for CZ. The text from the protocol is presented in normal font. The country-specific requirements or procedures are presented below in **bold**.

Section 8.1 **Overview**

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 experienced in treating AD and have documented experience and/or training in use of the assessments required by the protocol and must be either a physician, a certified physician's assistant, or an advanced registered nurse practitioner.

In CZ, according to Act no. 378/2007 Coll., only a physician can be an investigator.

12.5.3 Specific requirements for France

This section describes requirements and procedures that are specific only for FR. The text from the protocol is presented in normal font. The country-specific requirements or procedures are presented below in **bold**.

Section 5.2 **Inclusion criteria** In FR, the following inclusion criterion is to be added: • **Subject affiliated with or a beneficiary of a social security scheme.**
Section 8.2.1 **Demographics** • Ethnic origin (self-reported by the subject): 'Hispanic or Latino', 'not Hispanic or Latino', not reported (not provided or available). • Race (self-reported by the subject, more than 1 race may be reported): American Indian or Alaska native, Asian Japanese, Asian Chinese, Asian other, Black or African American, native Hawaiian or other Pacific Islander, White, not reported (not provided or available). **In FR, race and ethnicity data will not be collected from the subjects.**

12.5.4 Specific requirements for Japan

This section describes requirements and procedures that are specific only for JP. The text from the protocol is presented in normal font. The country-specific requirements or procedures are presented below in **bold**.

Section 5.2 **Inclusion criteria**

Inclusion criterion #2

18–75 years old (both included) at screening (Visit 1).

In JP, inclusion criterion #2 will be: **Japanese adults, 18–75 years old (both included) at screening (Visit 1)**.

Inclusion criterion #10

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

* A woman of childbearing potential is defined as a female subject aged ≥12 years or a younger girl who, at the discretion of the investigator, is deemed to be of reproductive potential. A woman is defined as not being of childbearing potential if she is postmenopausal (at least 12 months with no menses prior to screening without an alternative medical cause), 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, IUD, 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 vasectomized partner (given that the subject is monogamous).

In JP, ** will be: 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, IUD, IUS, combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral), sexual abstinence (when this is in line

with the preferred and usual lifestyle of the subject and not just being without a current partner), same-sex partner, or vasectomized partner (given that the subject is monogamous).
Section 5.3 **Exclusion criteria** Exclusion criterion #8 Positive HBsAg or positive anti-HCV AND positive HCV-RNA at screening. - Subjects with a negative HBsAg and a positive anti-HBc or anti-HBs at screening will have reflex testing for HBV-DNA. Subjects who have HBV-DNA above LLQ will be excluded. **In JP, in addition to the above, repeat HBV-DNA testing must be done at trial Weeks 8, 16 and 32 for Japanese subjects who at screening have a negative HBV-DNA reflex test (i.e. below LLQ), and** **- Negative HBsAg, negative anti-HBc, positive anti-HBs and without documentation of prior HBV vaccination** **or** **- Negative HBsAg and positive anti-HBc.** **If HBV-DNA is above LLQ at Week 8 subjects must discontinue IMP.** **Japanese subjects who at screening have a negative HBV-DNA reflex test (i.e. below LLQ), negative HBsAg, negative anti-HBc, positive anti-HBs and provide documentation of prior HBV vaccination will not require regular monitoring by HBV-DNA repeat testing in the trial.**
Section 6.8.2 **Storage and accountability of trial products** The investigator or authorized site staff is responsible for IMP accountability, and record maintenance (e.g. receipt, and final disposition records). **In JP, the Head of Institute will be responsible for the IMPs at the trial site.**
Section 6.10 **Reporting product complaints** Global Safety, LEO Pharma contact information for reporting product complaints: E-mail address: drug.safety@leo-pharma.com.

In JP, product complaints must be reported to Pharmacovigilance, LEO Pharma K.K. using the contact information below: **E-mail address: clinical_trial_jp@leo-pharma.com.** **Fax number: +81 3 4243 3311.** **Note: Reports sent to the above email address and fax number will be manually forwarded to Global Safety, LEO Pharma.**
Section 8.1 **Overview** 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 experienced in treating AD and have documented experience and/or training in use of the assessments required by the protocol and must be either a physician, a certified physician's assistant, or an advanced registered nurse practitioner. **In JP, principal investigators must be board-certified dermatologists.**
Section 10.5 **Pregnancy** The completed pregnancy forms must be faxed or scanned and e-mailed to Global Safety at LEO Pharma. Contact details are given in Section 12.2.5. **In JP, any pregnancy must be reported to Pharmacovigilance, LEO Pharma K.K. using the contact information below:** **E-mail address: clinical_trial_jp@leo-pharma.com.** **Fax number: +81 3 4243 3311.** **Note: Reports sent to the above email address and fax number will be manually forwarded to Global Safety, LEO Pharma.**
Section 12.2.5, Appendix 1 **Investigator reporting responsibilities** Contact details for Global Safety at LEO Pharma as stated in Section 12.2.5 are as follows: Global Safety at LEO Pharma E-mail address: drug.safety@leo-pharma.com. Fax number: +45 6910 2468.

In JP, SAEs must be reported to Pharmacovigilance, LEO Pharma K.K. using the contact information below: **E-mail address: clinical_trial_jp@leo-pharma.com.** **Fax number: +81 3 4243 3311.** **Note: Reports sent to the above email address and fax number will be manually forwarded to Global Safety, LEO Pharma.**
Section 12.2.5, Appendix 1 **LEO Pharma reporting responsibilities** Global Safety at LEO Pharma will notify the regulatory authorities and concerned investigators of SAEs according to the current applicable legislation for the concerned countries. **In JP, Pharmacovigilance, LEO Pharma K.K. will notify the regulatory authorities and concerned investigators of SAEs.**

12.5.5 Specific requirements for the United Kingdom

This section describes requirements and procedures that are specific only for the UK.
The text from the protocol is presented in normal font. The country-specific requirements or procedures are presented below in **bold**.

Section 6.8.4 **Trial product destruction** In the UK, the following clarification is to be added: All IMP (i.e. used, partly used, and unused vials) must be returned to the CMO, where it will be destroyed according to approved procedures and/or local requirements. **Alternatively, if due to local requirements used vials cannot be returned to the CMO, used vials can be destroyed at the trial site, provided the trial site has procedures in place for such IMP destruction.**

12.6 Appendix 6: Contact list

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

Sponsor

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

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

Coordinating investigator

Stephan Weidinger, MD.
Department of Dermatology and Allergy.
University Hospital Schleswig-Holstein.
Arnold-Heller-Str. 3.
24105 Kiel, Germany.

12.7 Appendix 7: Pandemic contingency plan (e.g. COVID-19)

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 (or any 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 minimize subject exposure 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 randomization 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.
- POEM, DLQI, EQ-5D-5L, WPAI-SHP, HADS, PGI-S, and PGI-I 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.

Reporting in eCRF

It will be recorded in the eCRF if a visit was conducted remotely (phone visit) and the reason why it was done remotely (due to COVID-19 or for other reasons). If the visit was not conducted at all, the reason will also be recorded in the eCRF.

12.8 Appendix 8: Protocol amendment history

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

Amendment 1 (05-Feb-2024, non-substantial, local UK)

Overall rationale for the amendment

The main purpose of this protocol amendment was to clarify aspects related to destruction of IMP specific for the UK. Changes to the protocol are summarized in the table below.

Section no. and title	Description of change	Brief rationale
Section 12.5.5 Specific requirements for the United Kingdom	In the UK, Section 6.8.4 has been updated to allow destruction of IMP at sites.	To clarify procedures for IMP destruction.
Section 12.8 Appendix 8: Protocol amendment history	Section updated. Amendment 1 (13-Nov-2023, non-substantial, global) has been moved from Protocol amendment summary of changes to Section 12.8.	Administrative change.

Abbreviations: please refer to the list of abbreviations.

Amendment 1 (13-Nov-2023, non-substantial, global)

This amendment is considered to be non-substantial based on the criteria set forth in Article 2 (13) of Regulation 536/2014 of the European Parliament and the Council of the European Union or subsequent regulation because it neither is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

Overall rationale for the amendment

The main purpose of this protocol amendment was to introduce qualitative interviews that will be performed as other assessments at selected trial sites. This global protocol amendment also includes some changes implemented in the local (European Union and Japan) protocol amendments and will serve as global consolidated protocol for the trial going forward. Changes to the protocol are summarized in the table below (text added to the protocol is written in **bold** and deleted text has a line through it).

Section no. and title	Description of change	Brief rationale
Section 1.3 Schedule of activities	Panel 2: Schedule of trial activities, footnote o) related to vital signs was edited: **Vital signs must be assessed prior to IMP administration. In addition**, at Weeks 0, 1, 2, 3, and 4, subjects will be monitored after IMP administration for potential immediate drug reactions for a minimum of 2 hours with vital signs taken immediately (within 5 minutes) after last IMP administration as well as after 30 minutes (± 5 minutes), after 1 hour (± 5 minutes), and after 2 hours (± 5 minutes), or until stable, whichever is later.	To specify vital signs assessment procedure.
Section 1.3 Schedule of activities	Panel 2: Schedule of trial activities **Other assessments: Qualitative interviews in CA, UK and US** were added with reference to Section 8.7.2 as: **Scheduling interview** at Week 10 (Visit 10) **Clinigma to conduct trial interviews** at Week 14 (Visit 12).	To add qualitative interviews as other assessments.
	Panel 2: Schedule of trial activities, footnote t) related to scheduling and conduction of the interviews was added: **Interviews will be conducted at selected trial sites. The interview will be scheduled to occur as soon as possible and within 14 days after Week 14 (Visit 12).**	To add qualitative interviews as other assessments.
Section 5.3 Exclusion criteria	Exclusion criterion #7 **Non-serious** skin infection within 7 days prior to baseline. *NOTE: Subject may be rescreened (once) after infection resolves. However, rescreening will require approval by the sponsor's medical expert (see Section 5.4).*	Updated due to authority request in the EU CTIS clinical trial application procedure.
	Exclusion criterion #10 Evidence of active or latent tuberculosis according to local standard of care for patients requiring initiation of a biologic treatment. - A tuberculosis test can be performed at the central or local laboratory. **Subjects with a positive or indeterminate test at screening will be excluded. *NOTE: Subject may be retested (once) if the initial test was indeterminate.***	To clarify exclusion of subjects with indeterminate tuberculosis test.
	Exclusion criterion #12 **Uncontrolled/untreated clinically significant depression or** history of attempted suicide or is at significant risk of suicide (either in the opinion of the investigator or defined as a "yes" to suicidal ideation questions no. 4 or 5 or answering "yes" to suicidal behavior on the C-SSRS Screening version).	Updated due to authority request in the EU CTIS clinical trial application procedure.
	Exclusion criterion #25 Receipt of live attenuated vaccines 30 days prior to baseline **or longer if recommended so by local guidelines**.	Updated due to authority request in the EU CTIS clinical trial application procedure.
Section 6.2 Administration of IMP	'IMP will be administered by ~~a~~ qualified, unblinded ~~HCP~~ **site staff** as the active drug is visually distinct from placebo…'.	To specify IMP administration procedure.
Section 6.3.2 Blinding	'IMP will be prepared, handled, and administered by ~~a~~ qualified, unblinded ~~HCP~~ **site staff** ~~at the site~~ who will not be involved in the management…'.	To specify IMP administration procedure.

Section no. and title	Description of change	Brief rationale
	'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~~ **site staff** ~~at the site~~ will contact the…'.	
Section 6.7 Prohibited medications and procedures	4. Use of UVA or UVB, PUVA, other phototherapy, ~~or~~ tanning beds**, or prolonged sun exposure**.	Updated due to authority request in the EU CTIS clinical trial application procedure.
Section 6.8.3 Treatment compliance	'IMP injections will be performed by unblinded ~~HCP~~ **site staff** who will also keep…'.	To specify IMP administration procedure.
Section 7.2.2 Reasons for temporary discontinuation of IMP	In case an urgent situation requires immediate action, IMP dosing may be temporary discontinued if, at the investigator's discretion, 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. **A decision to re-initiate IMP must always be discussed with and approved by the sponsor's medical expert.**	Updated due to authority request in the EU CTIS clinical trial application procedure.
Section 8.4.1 Vital signs	Vital signs (resting BP, pulse, and body temperature) must be assessed **prior to IMP administration** according to the schedule of trial activities (Section 1.3).	To specify vital signs assessment procedure.
Section 8.4.5.1 Overview	Panel 12: Clinical laboratory tests, footnote 3) related to hepatitis B, hepatitis C and HIV was edited: Conducted at screening ~~only~~.	Edited to align with EU and Japanese authority requests for additional assessments of hepatitis.
Section 8.7.2 Qualitative interviews (selected sites)	Section added to describe the procedure for conducting qualitative interviews.	To provide guidance for performing qualitative interviews.
Section 12.2.4 Recording and follow-up of AEs	Text added to describe recording of potential AEs reported by the subjects during qualitative interviews.	To provide guidance on handling of AEs reported during interviews.
Section 12.5.1 Specific requirements for all EU countries	In CZ, DE, ES, FR, HU, PL and RO, Panel 2: Schedule of trial activities has been updated with regards to additional assessments of vital signs, hepatitis B, hepatitis C, and chemistry and hematology. Panel 18 Schedule of trial activities for EU countries was added.	Updated due to authority request in the EU CTIS clinical trial application procedure.
	In CZ, DE, ES, FR, HU, PL and RO, Section 2.4 has been updated with regards to additional assessments of vital signs.	Updated due to authority request in the EU CTIS clinical trial application procedure.

Section no. and title	Description of change	Brief rationale
Section 12.5.1 Specific requirements for all EU countries	In CZ, DE, ES, FR, HU, PL and RO, exclusion criteria #8, #14, #15 and #30 (Section 5.3) have been updated. Section 12.5.1.2 Eligibility criteria specific for EU countries was added.	Updated due to authority request in the EU CTIS clinical trial application procedure.
	In CZ, DE, ES, FR, HU, PL and RO, Section 6.2 has been updated with regards to additional assessments of vital signs.	Updated due to authority request in the EU CTIS clinical trial application procedure.
	In CZ, DE, ES, FR, HU, PL and RO, Section 7.2.1 has been updated with regards to additional assessments of hepatitis B and hepatitis C.	Updated due to authority request in the EU CTIS clinical trial application procedure.
	In CZ, DE, ES, FR, HU, PL and RO, Section 8.4.1 has been updated with regards to additional assessments of vital signs.	Updated due to authority request in the EU CTIS clinical trial application procedure.
	In CZ, DE, ES, FR, HU, PL and RO, Section 8.4.5.2 has been updated with regards to pregnancy testing procedure.	Updated due to authority request in the EU CTIS clinical trial application procedure.
Section 12.5.2 Specific requirements for Czech Republic	In CZ, Section 8.1 has been updated in accordance with applicable local laws and regulations.	Updated due to authority request in the EU CTIS clinical trial application procedure.
Section 12.5.3 Specific requirements for France	In FR, Section 8.2.1 has been updated in accordance with applicable local laws and regulations.	Updated due to authority request in the EU CTIS clinical trial application procedure.
Section 12.5.4 Specific requirements for Japan	In JP, inclusion criterion #10 (Section 5.2) and exclusion criterion #8 (Section 5.3) have been updated.	Updated due to Japanese authority request.
Section 12.8 Appendix 8: Protocol amendment history	Section added. Classification of previous EU amendments with reference to Article 10(a) of Directive 2001/20/EC has been corrected to refer to Article 2 (13) of EU Clinical Trial Regulation 536/2014.	To list all the country-specific amendments preceding this global amendment.
Throughout document	Wording ‘rescue medication’ changed to ‘rescue treatment’.	For consistency.

Section no. and title	Description of change	Brief rationale
Throughout document	Minor editorial revisions including references to respective subsections of Section 12.5 for details on the country-specific requirements and procedures.	Minor, have therefore not been summarized.

Abbreviations: please refer to the list of abbreviations.

Amendment 3 (05-Oct-2023, non-substantial, local Czech Republic, Germany, France, Hungary, Poland, Romania and Spain)

This amendment is considered to be non-substantial based on the criteria set forth in Article 2 (13) of Regulation 536/2014 of the European Parliament and the Council of the European Union or subsequent regulation because it neither is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

Overall rationale for the amendment

The main purpose of this protocol amendment was to address the request from the regulatory authorities of the European Union countries included in this trial via the Clinical Trials Information System procedure after their review of the European Union protocol version 2.0. Changes to the protocol are summarized in the table below (text added to the protocol is written in **bold**).

Section no. and title	Description of change	Brief rationale
Section 5.3 Exclusion criteria	Exclusion criterion #7 **Non-serious** skin infection within 7 days prior to baseline. *NOTE: Subject may be rescreened (once) after infection resolves. However, rescreening will require approval by the sponsor's medical expert (see Section 5.4).*	Added due to authority request.
Section 5.3 Exclusion criteria	Exclusion criterion #12 **Uncontrolled/untreated clinically significant depression or** history of attempted suicide or is at significant risk of suicide (either in the opinion of the investigator or defined as a "yes" to suicidal ideation questions no. 4 or 5 or answering "yes" to suicidal behavior on the C-SSRS Screening version).	Added due to authority request.
Section 12.8 Appendix 8: Protocol amendment history	This section has been updated. Amendment 2 has been moved from Protocol amendment summary of changes to Section 12.8.	Administrative change.
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarized.

Amendment 2 (28-Sep-2023, non-substantial, local France)

This amendment is considered to be non-substantial based on the criteria set forth in Article 2 (13) of Regulation 536/2014 of the European Parliament and the Council of the European Union or subsequent regulation because it neither is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

Overall rationale for the amendment

The main purpose of this protocol amendment was to address the request from the French Committees of Protection of Persons (Comités de Protection des Personnes, CPP) via the Clinical Trials Information System procedure. Changes to the protocol are summarized in the table below (text added to the protocol is written in **bold**).

Section no. and title	Description of change	Brief rationale
Section 5.4 Screening and subjects excluded prior to randomization	• Date of birth (day, month, and year; only month and year; or only year, as per local legislation), age, sex, ethnicity, race **(for details on the country-specific requirements, see Section 12.5)**.	Added as requested.
Section 8.2.1 Demographics	• Ethnic origin (self-reported by the subject): 'Hispanic or Latino', 'not Hispanic or Latino', not reported (not provided or available). **For details on the country-specific requirements, see Section 12.5.** • Race (self-reported by the subject, more than 1 race may be reported): American Indian or Alaska native, Asian Japanese, Asian Chinese, Asian other, Black or African American, native Hawaiian or other Pacific Islander, White, not reported (not provided or available). **For details on the country-specific requirements, see Section 12.5.**	Added as requested.
Section 12.1.5 Data protection	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. **For details on the country-specific requirements for personal data collection, see Section 12.5.**	Added as requested.
Section 12.5 Appendix 5: Country-specific requirements	**In France, race and ethnicity data will not be collected from the subjects.**	Added as requested.
Section 12.8 Appendix 8: Protocol amendment history	This section has been added. Amendment 1 has been moved from Protocol amendment summary of changes to Section 12.8.	Administrative change.

Section no. and title	Description of change	Brief rationale
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarized.

Amendment 1 (16-Sep-2023, non-substantial, local Czech Republic, Germany, France, Hungary, Poland, Romania and Spain)

This amendment is considered to be non-substantial based on the criteria set forth in Article 2 (13) of Regulation 536/2014 of the European Parliament and the Council of the European Union or subsequent regulation because it neither is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

Overall rationale for the amendment

The main purpose of this protocol amendment was to address requests from the regulatory authorities of the European Union countries included in this trial via the Clinical Trials Information System procedure after their review of the global protocol v1.0. Changes to the protocol are summarized in the table below (text added to the protocol is written in **bold** and deleted text has a line through it).

Section no. and title	Description of change	Brief rationale
Section 1.3 Schedule of activities	Panel 2: Schedule of trial activities Assessments of vital signs were added for Week 6 (Visit 8), Week 10 (Visit 10), and Week 14 (Visit 12). Panel 2: Schedule of trial activities, footnote o) related to vital signs was edited: At Weeks 0, 1, 2, 3, and 4, subjects will be monitored after IMP administration for potential immediate drug reactions for a minimum of 2 hours with vital signs taken immediately (within 5 minutes) after last IMP administration as well as after 30 minutes (± 5 minutes), after 1 hour (± 5 minutes), and after 2 hours (± 5 minutes), or until stable, whichever is later. **From Week 5 onwards, subjects will be monitored after IMP administration for potential immediate drug reactions for a minimum of 20 minutes with vital signs assessed within 5 minutes**	Added as requested.

Section no. and title	Description of change	Brief rationale
	after last IMP administration as well as after 20 minutes (± 5 minutes), or until stable, whichever is later.	
Section 1.3 Schedule of activities	Panel 2: Schedule of trial activities Assessments of hepatitis B, hepatitis C and HIV were added for Week 12 (Visit 11) and Week 24 (Visit 15). Panel 2: Schedule of trial activities, footnote p) related to hepatitis B, hepatitis C and HIV was added: **For subjects who at screening have a negative HBV-DNA reflex test (i.e. HBV-DNA is not detected), and negative HBsAg, negative anti-HBc, positive anti-HBs and without documentation of prior HBV vaccination or negative HBsAg and positive anti-HBc, repeat HBV-DNA will be done at Weeks 12 and 24. For subjects who at screening have positive anti-HCV but negative HCV-RNA (i.e. HCV-RNA is not detected), repeat HCV-RNA will be done at Weeks 12 and 24.**	Added as requested.
Section 1.3 Schedule of activities	Panel 2: Schedule of trial activities Assessments of chemistry and hematology (central laboratory) were added for Week 1 (Visit 4), Week 2 (Visit 5), and Week 3 (Visit 6).	Added as requested.
Section 2.4 Ethical considerations	In addition, at Weeks 0, 1, 2, 3, and 4, subjects will be monitored for a period of 2 hours to detect potential immediate drug reactions**, and from Week 5 onwards, subjects will be monitored for a period of 20 minutes**.	Added as requested for additional assessments of vital signs.
Section 5.3 Exclusion criteria	Exclusion criterion #8 Positive HBsAg or positive anti-HCV AND positive HCV-RNA at screening. - Subjects with a negative HBsAg and a positive anti-HBc or anti-HBs at screening will have reflex testing for HBV-DNA. **Subjects who have a positive HBV-DNA test (i.e. HBV-DNA is detected) will be excluded.** **- For subjects who at screening have a negative HBV-DNA reflex**	Added as requested.

Section no. and title	Description of change	Brief rationale
	test (i.e. HBV-DNA is not detected), and **Negative HBsAg, negative anti-HBc, positive anti-HBs and without documentation of prior HBV vaccination** **or** **Negative HBsAg and positive anti-HBc** **repeat HBV-DNA testing must be done at Weeks 12 and 24. If HBV-DNA is positive (i.e. HBV-DNA is detected) at Week 12, subjects must permanently discontinue IMP.** **- Subjects who at screening have a negative HBV-DNA reflex test (i.e. HBV-DNA is not detected), negative HBsAg, negative anti-HBc, positive anti-HBs and provide documentation of prior HBV vaccination will not require regular monitoring by HBV-DNA repeat testing in the trial.** **- For subjects who at screening have positive anti-HCV but negative HCV-RNA (i.e. HCV-RNA is not detected), repeat HCV-RNA will be done at Weeks 12 and 24. If HCV-RNA is positive (i.e. HCV-RNA is detected) at Week 12, subjects must permanently discontinue IMP.**	
Section 5.3 Exclusion criteria	Exclusion criterion #14 Any disorder* at screening and/or baseline, which is not stable in the opinion of the investigator, and could: -Affect the safety of the subject throughout the trial. - Influence the results of the trial. - Impede the subject's ability to complete the trial.	Added as requested.

Section no. and title	Description of change	Brief rationale
	[redacted]	
Section 5.3 Exclusion criteria	Exclusion criterion #15 Any significant abnormal finding* at screening and/or baseline which may in the opinion of the investigator: - Put the subject at risk because of their participation in the trial. - Influence the results of the trial. - Influence the subject's ability to complete the trial. *The abnormal finding must be clinically significant and observed during the screening period. Examples include **but are not limited to** abnormal findings in physical examination, vital signs, ECG, hematology **(e.g. hemoglobin <100 g/L, neutrophils <1.5 x 10^9/L, thrombocytes <75 x 10^9/L)**, biochemistry **(e.g. serum creatinine >1.5 times the ULN, bilirubin >1.5 times the ULN; subjects with a history of Gilbert's syndrome are eligible for this trial provided direct bilirubin is < the ULN)**, or urinalysis.	Added as requested.
Section 5.3 Exclusion criteria	Exclusion criterion #25 Receipt of live attenuated vaccines 30 days prior to baseline **or longer if recommended so by local guidelines**.	Added as requested.
Section 5.3 Exclusion criteria	Exclusion criterion #30 Subjects who are legally institutionalized **or legally protected**	Clarified as requested.

Section no. and title	Description of change	Brief rationale
	(e.g. those under guardianship, curatorship, safeguard of justice) or other subjects incapable of giving informed consent according to the law of his/her residing country.	
Section 6.2 Administration of IMP	At Weeks 0, 1, 2, 3, and 4, subjects will be monitored for potential immediate drug reactions for a minimum of 2 hours after IMP administration. Vital signs will be taken immediately (within 5 minutes) after last IMP administration, as well as after 30 minutes (± 5 minutes), after 1 hour (± 5 minutes), and after 2 hours (± 5 minutes), or until stable, whichever is later. **From Week 5 onwards, subjects will be monitored after IMP administration for potential immediate drug reactions for a minimum of 20 minutes with vital signs assessed within 5 minutes after last IMP administration as well as after 20 minutes (± 5 minutes), or until stable, whichever is later.** Vital signs will be documented in the eCRF.	Added as requested for additional assessments of vital signs.
Section 6.7 Prohibited medications and procedures	4. Use of UVA or UVB, PUVA, other phototherapy, ~~or~~ tanning beds**, or prolonged sun exposure**.	Added as requested.
Section 7.2.1 Reasons for permanent discontinuation of IMP	Added to the list: **• Positive HBV-DNA test (i.e. HBV-DNA is detected) at Week 12 (see exclusion criterion no. 8).** **• Positive HCV-RNA test (i.e. HCV-RNA is detected) at Week 12 (see exclusion criterion no. 8).**	Added as requested.
Section 7.2.2 Reasons for temporary discontinuation of IMP	In case an urgent situation requires immediate action, IMP dosing may be temporary discontinued if, at the investigator's discretion, 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. **A decision to re-initiate IMP must always be discussed with and approved by the sponsor's medical expert.**	Added as requested.
Section 8.4.1 Vital signs	At Weeks 0, 1, 2, 3, and 4, subjects will be monitored after IMP	Added as requested for additional assessments of vital signs.

Section no. and title	Description of change	Brief rationale
	administration for immediate drug reactions for a minimum of 2 hours with vital signs taken immediately (within 5 minutes) after last IMP administration, after 30 minutes (± 5 minutes), after 1 hour ± 5 minutes), and after 2 hours ± 5 minutes), or until stable, whichever is later. **From Week 5 onwards, subjects will be monitored after IMP administration for potential immediate drug reactions for a minimum of 20 minutes with vital signs assessed within 5 minutes after last IMP administration as well as after 20 minutes ± 5 minutes), or until stable, whichever is later.**	
Section 8.4.5.1 Overview	Panel 12: Clinical laboratory tests, footnote 3) related to hepatitis B, hepatitis C and HIV was edited: Conducted at screening ~~only~~.	Edited as requested for additional assessments of hepatitis.
Section 8.4.5.2 Investigator evaluation of laboratory samples	If the urine pregnancy test is positive but not confirmed by ~~the~~ **repeated** serum pregnancy test, the subject may continue IMP treatment, but the LEO medical expert should be consulted.	Added as requested.
Section 12.5 Appendix 5: Country-specific requirements	Information added for the Czech Republic regarding Section 8.1 Overview **In Czech Republic, according to Act no. 378/2007 Coll., only a physician can be an investigator.**	Added as requested and to comply with Act no. 378/2007 Coll..
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarized.

Amendment 1 (12-Jul-2023, non-substantial, local Japan)

This protocol amendment was to address comments from the Health Authority in Japan after their review of the global protocol v1.0. The purpose of the amendment was mainly to clarify aspects related to the inclusion and exclusion criteria. Changes to the protocol are summarized in the table below.

Section no. and title	Description of change	Brief rationale
Section 12.5 Appendix 5: Country-specific requirements	Inclusion criterion #10 The definition of highly effective form of birth control was updated. The following contraception methods were removed from the definition:	Deleted as requested.

Section no. and title	Description of change	Brief rationale
	• Combined (oestrogen and progestogen) hormonal contraceptives (~~intravaginal and transdermal~~) with ovulation inhibitory effects. • ~~Progestogen-only hormonal contraceptives (oral, intravaginal, or transdermal) that suppress ovulation~~. Exclusion criterion #8 It was included that repeat HBV-DNA testing must be done at trial Weeks 8, 16 and 32 for Japanese subjects who at screening have a negative HBV-DNA reflex test (i.e. below LLQ), and - Negative HBsAg, negative anti-HBc, positive anti-HBs and without documentation of prior HBV vaccination or - Negative HBsAg and positive anti-HBc. If HBV-DNA is above LLQ at Week 8 subjects must discontinue IMP. Japanese subjects who at screening have a negative HBV-DNA reflex test (i.e. below LLQ), negative HBsAg, negative anti-HBc, positive anti-HBs and provide documentation of prior HBV vaccination will not require regular monitoring by HBV-DNA repeat testing in the trial.	Added as requested.

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