Cover Page

Study title: A Randomized, Double-blinded, Active Comparator-controlled, 16-week, Single-site, Exploratory, Mechanistic Trial to Assess the Effect of LEO 138559 on the Molecular Signature and Safety in Adults With Moderate to Severe Atopic Dermatitis.
LEO Pharma number: LP0145-2274
NCT number: NCT05470114
Date: 04-Jan-2023

Clinical trial protocol

LP0145-2274

A randomized, double-blinded, active comparator-controlled, 16-week, single-site, exploratory, mechanistic trial to assess the effect of LEO 138559 on the molecular signature and safety in adults with moderate to severe atopic dermatitis

Phase 2a - exploratory mechanistic trial

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

LEO Pharma A/S	**Trial ID:**	**LP0145-2274**
	Date:	**04-Jan-2023**
	EudraCT no:	**2021-006211-28**
	Version:	**5.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

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

PPD M.Sci., Ph.D
PPD

PPD MMath, PhD
PPD

PPD MD, DMSc
PPD

PPD MD, PhD
PPD

PPD MSc. Pharm.
PPD

Approval statement Signatory Investigator

Assoc.-Prof. PD PPD MD, MSc
Signatory investigator

Acknowledgement statement investigator(s)

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

Protocol amendment summary of changes table

Document history

Document	Date	Type of protocol amendment
Amendment 3 (substantial)	04-Jan-2023	Global
Amendment 2 (substantial)	14-Apr-2022	Global
Amendment 1 (substantial)	08-Mar-2022	Global
Original protocol	13-Jan-2022	NA

Amendment 3 (04-Jan-2023)

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

Overall rationale for the amendment:

A new serum biomarker in atopic dermatitis has been identified in the literature. This amendment is intended to include this new biomarker. In addition, this amendment is intended to clarify that randomization will be continued until 12 patients who are evaluable for the primary endpoint i.e., for whom lesional skin biopsies at baseline and week 4 are available, are included in the study.

Section no. and name	Description of change	Brief rationale
11.6.2 Blood biomarkers	**Addition of newly identified biomarker IL-22BP to the list of blood serum biomarkers that will be analysed.** **Formerly (First paragraph):** Evaluation of effects of treatment of AD patients with LEO 138559 or Dupixent® on protein biomarkers in blood, including but not limited to E- selectin, PI3/Elafin, CCL7, and IL-16, will be performed on serum samples. … **New:** Evaluation of effects of treatment of AD patients with LEO 138559 or Dupixent® on protein biomarkers in blood, including but not limited to E-selectin, PI3/Elafin, CCL7, and IL-16, **and newly identified IL-22BP** [50] will be performed on serum samples. …	**With the identification of a new blood serum biomarker for atopic dermatitis, LEO Pharma A/S has decided to add this biomarker to the set of biomarkers that will be analysed in this clinical trial.**
	Wording regarding the number of patients to be randomised rephrased:	**Originally a replacement of patients was planned if more than 3 patients left the study before the end of the 4th week of treatment.** **However, it was always the intention to achieve 12 subjects evaluable for the primary endpoint i.e., for whom a lesional biopsy is available at baseline and week 4.** **Wording has been revised for clarity.**

Section no. and name	Description of change	Brief rationale
Protocol Synopsis	**Formerly:** A total of 12 subjects will be randomised 2:1 to: • LEO 138559 (8 subjects). • Dupixent® (4 subjects). **New:** **Approximately** 12 subjects will be randomised 2:1 to: • LEO 138559 (8 subjects). • Dupixent® (4 subjects).	
7.2 Number of subjects needed	**Formerly:** … A total of 12 subjects will be randomised in a 2:1 ratio to LEO 138559 450 mg Q2W (8 subjects) and comparator 300 mg Q2W (4 subjects). In case more than 3 subjects prematurely terminate the trial before week 4, replacement of subjects may be considered after consultation with the sponsor. **New:** **…Approximately** 12 subjects will be randomised in a 2:1 ratio to LEO 138559 450 mg Q2W (8 subjects) and comparator 300 mg Q2W (4 subjects) **to be able to achieve 12 subjects evaluable for the primary endpoint i.e., for whom a lesional biopsy is available at baseline and week 4**. ~~In case more than 3 subjects prematurely terminate the trial~~	

Section no. and name	Description of change	Brief rationale
10.1 General principles	~~before week 4, replacement of subjects may be considered after consultation with the sponsor.~~ **The third paragraph of this section (**"Subjects who withdraw from the trial and subjects who permanently discontinue IMP can be considered to be replaced after consultation with the sponsor if withdrawal or permanent discontinuation in more than 3 subjects occurred before week 4. Otherwise, subjects will not be replaced."**) has been deleted without replacement**.	

Section no. and name	Description of change	Brief rationale
14.1 Sample size	**The wording regarding the sample size has been rephrased to precisely describe that it is intended to continue with randomisation until a number of 12 patients evaluable for the primary endpoint is achieved.** **Formerly:** The sample size of 12 subjects (8 receiving LEO 138559 and 4 receiving comparator) is based on the trial design for the exploratory comparison of the molecular signature changes of LEO 138559 and the comparator. The sample size is not based on power calculations. **New:** The sample size of 12 subjects **evaluable for the primary endpoint i.e., for whom a lesional biopsy is available at baseline and week 4** (8 receiving LEO 138559 and 4 receiving comparator) is based on the trial design for the exploratory comparison of the molecular signature changes of LEO 138559 and the comparator. The sample size is not based on power calculations.	

<table>
<tr><th>Section no. and name</th><th>Description of change</th><th>Brief rationale</th></tr>
<tr><td>4 Schedule of trial procedures</td><td>Link to footnote has been corrected

Formerly:

<table><tr><td></td><td>End of treatment[c)]</td></tr><tr><td>Skin biopsies[r)]</td><td>X[r)]</td></tr></table>…
r) Photographs will be taken of the biopsy sites prior to each biopsy sampling
s) Suture removal in week 18, i.e., 2 weeks after the last biopsy can either be performed on site or alternatively at general practitioner as being most convenient for the subject.

New:

<table><tr><td></td><td>End of treatment[c)]</td></tr><tr><td>Skin biopsies[r)]</td><td>X[r)]</td></tr></table>…
r) Photographs will be taken of the biopsy sites prior to each biopsy sampling
s) Suture removal in week 18, i.e., 2 weeks after the last biopsy can either be performed on site or alternatively at general practitioner as being most</td><td>In reviewing this amendment, it was noticed that the hyperlink to the footnote regarding the biopsy at the end of the treatment was incorrect. This mistake has been corrected now.</td></tr>
</table>

Table of contents

List of panels

List of abbreviations

AAD	American Academy of Dermatology
AD	atopic dermatitis
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BSA	body surface area
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CMO	contract manufacturing organisation
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRO	contract research organisation
CTR	clinical trial report
EASI	Eczema Area and Severity Index
EASI50	at least 50% reduction in EASI score
EASI75	at least 75% reduction in EASI score
EASI90	at least 90% reduction in EASI score
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FU	follow-up visit
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HB	hepatitis B
HCP	healthcare professional
HIV	human immunodeficiency virus

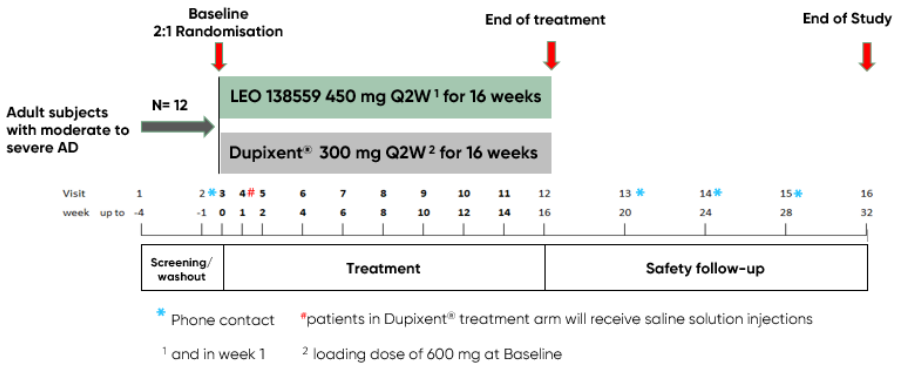
HV	Healthy volunteer
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IEC	independent ethics committee
IFN	interferon
IGA	investigator global assessment
IL-22BP	interleukin 22 binding protein
IMP	investigational medicinal product
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JAK	janus kinase
KLH	keyhole limpet hemocyanin
LOCF	last observation carried forward
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MoA	mode of action
NA	not applicable
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
NBUVB	narrow band ultraviolet B
PD	pharmacodynamics
PDE-4	phosphodiesterase-4
PK	pharmacokinetics
PPD	purified protein derivative
PRO	patient-reported outcome
PT	preferred term
PUVA	psoralen + ultraviolet A
Q2W	every second week
QT	QT interval, time from start of the Q wave to the end of the T wave on an ECG tracing

RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SD	standard deviation
SmPC	summary of product characteristics
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TCI	topical calcineurin inhibitor(s)
TCS	topical corticosteroid(s)
Th2	T-helper 2
UVA1	ultraviolet A1
UVB	ultraviolet B
vIGA-AD	validated Investigator Global Assessment Scale for Atopic Dermatitis
WHO	World Health Organization

1 Protocol synopsis

<table>
<tr><td>Trial ID
EudraCT no</td><td>LP0145-2274
2021-006211-28</td></tr>
<tr><td>Title of trial</td><td>A randomized, double-blinded, active comparator-controlled, 16-week, single-site, exploratory, mechanistic trial to assess the effect of LEO 138559 on the molecular signature and safety in adults with moderate to severe atopic dermatitis.</td></tr>
<tr><td>Short title of trial</td><td>A multi-omics disease signature trial in adult patients with moderate - severe AD</td></tr>
<tr><td>Main objectives, and endpoints</td><td>
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary objective</td><td>Primary endpoint</td></tr>
<tr><td>To investigate the molecular signature changes in subjects with moderate to severe atopic dermatitis (AD) following treatment with LEO 138559 and Dupixent®</td><td>• Change in biomarkers typically associated with atopic dermatitis in lesional skin biopsies from baseline to week 4.</td></tr>
<tr><td>Secondary objective</td><td>Secondary endpoints</td></tr>
<tr><td>To evaluate the safety of LEO 138559 in subjects with moderate to severe AD</td><td>Secondary endpoint
• Number of treatment-emergent adverse events from baseline to week 16 per subject.
Exploratory endpoint (ADA)
• Having a positive ADA response at weeks 0, 4, 8, 12, 16, 32, assessed separately.</td></tr>
<tr><td>Exploratory objectives</td><td>Exploratory endpoints</td></tr>
<tr><td>To evaluate the efficacy of LEO 138559 and Dupixent® in subjects with moderate to severe AD</td><td>Exploratory endpoints (efficacy)
• Change in EASI score from baseline to week 1, 2, 4, 6, 8, 12, and 16.
• Having a decrease in EASI of at least 50% (EASI 50) from baseline to week 1, 2, 4, 6, 8, 12, and 16, assessed separately.
• Having a decrease in EASI of at least 75% (EASI 75) from baseline to week 1, 2, 4, 6, 8, 12, and 16, assessed separately.
• Having a decrease in EASI of at least 90% (EASI 90) from baseline to week 1,</td></tr>
</table>
</td></tr>
</table>

		2, 4, 6, 8, 12, and 16, assessed separately. • Having vIGA-AD score of 0 (clear) or 1 (almost clear) at week 1, 2, 4, 6, 8, 12, and 16, assessed separately. • Change in Worst Daily Pruritus NRS (weekly average) from baseline to weeks 1, 2, 4, 6, 8, 12, and 16.
	To evaluate the pharmacokinetics of LEO 138559 in subjects with moderate to severe AD	• Serum concentration of LEO 138559 at weeks 0, 1, 4, 8, 12, 16, and 32.
	To evaluate the effect of treatment with LEO 138559 or Dupixent® on disease biomarkers in subjects with moderate to severe AD	• Change in expression of AD disease biomarkers in skin biopsies from baseline to week 1 and 16. • Change in expression of additional AD disease biomarkers in serum from baseline to week 1, 4, and 16. • Change in expression of additional AD disease biomarkers in skin tape strips from baseline to week 1, 4, and 16.
Final collection of data for the primary endpoint	Visit 6 (week 4)	
Trial design	LP0145-2274 is a phase 2a randomized, double-blinded, active comparator-controlled, single-site trial conducted in Austria. The screening phase of up to 4 weeks (weeks -4 to 0) includes a washout phase of 7 days (week -1 to 0). Subjects must stop treatment with topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), topical phosphodiesterase (PDE)-4 inhibitors, or other topical prescription treatments 1 week prior to baseline. Washout periods for systemic treatments will be checked at the screening visit. At baseline, subjects will be randomised to one of two treatment groups. Treatments will be administered at the trial site in a Q2W dosing schedule during the treatment period of 16 weeks. While subjects in the LEO 138559 treatment group will receive additional dosing at week 1 visit, subjects in the comparator group will receive injections with saline solution at this visit for blinding purposes. During a safety follow-up period of 16 weeks after end of treatment 3 phone contacts and a safety follow-up visit (week 32) will be performed.	

	
Main assessments	• Differentially expressed genes via single cell RNA sequencing (scRNASeq) from lesional skin biopsies • Multi-omics from lesional tape stripping and serum • Adverse events • Vital signs (resting blood pressure, pulse, and body temperature) • Physical examination • ECG (12-lead resting digital ECG) • Central / Local laboratory testing (haematology, blood chemistry, serology, pregnancy test).
Main criteria for inclusion	• 18 – 64 years old at screening (both included). • Diagnosis of AD [as defined by the American Academy of Dermatology (AAD) Consensus Criteria] that has been present for ≥1 year prior to screening. • Subjects who have a recent history (within 6 months before screening) of inadequate response to treatment with topical medication, or for whom topical treatments are otherwise medically inadvisable. • EASI score ≥12 at screening and ≥16 at baseline. • vIGA-AD score ≥3 at screening and baseline. • Body surface area (BSA) of AD involvement ≥10% at screening and baseline. • Worst Daily Pruritus NRS (weekly average) of ≥3 points at baseline.
Main criteria for exclusion	• Treatment with systemic immunosuppressive/immunomodulating medication (excluding systemic antihistamines if taken at stable dose already before baseline), e.g., JAK inhibitors, immunoglobulin/blood products, or phototherapy within 2 weeks or 5 half-lives prior to baseline, whichever is longer. • Treatment with systemic corticosteroids within 4 weeks prior to baseline (NOTE: Inhaled or intranasal steroids equivalent to doses including and up to 500 µg beclometasone (or equivalent) daily is allowed). • Treatment with biologics within 5 half-lives (if known) or 16 weeks prior to baseline, whichever is longer. • Treatment with TCS, TCI, or topical PDE-4 inhibitor within 1 week prior to baseline (NOTE: Patient may be rescreened (one time) if failed for this criterion. • Intake of nonsteroidal anti-inflammatory drugs (NSAIDs) within 1 week prior to baseline. Intake of paracetamol will be allowed.

	• Treatment with a live (attenuated) vaccine within 12 weeks prior to baseline. • Clinically significant active chronic or acute infection requiring systemic treatment within 4 weeks prior to baseline that may compromise the safety of the subject. • Clinically significant abnormalities detected on vital signs or ECG (apart from 1st degree atrioventricular (AV) block that is allowed). • Serious heart conditions, chronic lung diseases. • Acute asthma, acute bronchospasm, moderate to severe asthma. • Skin infection within 1 week prior to the baseline visit. • Presence of hepatitis B or C infection at screening. • Active inflammatory bowel disease (IBD) or history of IBD, anaphylaxis, immune complex disease, pancreatic disease or known or suspected history of immunosuppressive disorder. • History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening. • Subject has a positive test for tuberculosis at screening. • Subject is pregnant or lactating.
Investigational medicinal products	**Test Drug:** • Name of IMP: LEO 138559 • Active substance: LEO 138559 • Dosage form: Lyophilised powder for reconstitution (using 1.0 mL sterilised water) adding up to a volume of 1.2 mL/vial • Concentration: 150 mg/mL • Dose and frequency: 450 mg once every 2 weeks (Q2W) i.e., 3 injections per administration. In addition to the Q2W dosing schedule during the treatment phase, subjects randomised to LEO 138559 treatment group will receive a dose of LEO 138559 at visit 4 (week 1) • Method of administration: Subcutaneous. **Comparator:** • Name of IMP: Dupixent® • Active substance: dupilumab • Dosage form: Solution for injection, 2 mL prefilled syringe • Concentration: 150 mg/mL • Dose and frequency: Initial 600 mg once (administered as two 300 mg injections) followed by 300 mg Q2W (to compensate for the difference in treatment regimen between test drug and comparator, subjects randomised to Dupixent® will receive additional injections with saline solution). • Method of administration: Subcutaneous.

Duration of trial participation	Up to 36 weeks in total:

	• Up to 4 weeks screening period including a washout phase of 1 week (week -1 to 0). • 16 weeks treatment period • 16 weeks safety follow-up
Number of subjects	Approximately 12 subjects will be randomised 2:1 to: • LEO 138559 (8 subjects). • Dupixent® (4 subjects).
Number and distribution of trial sites	Single site study performed in Austria
Statistical methods	All endpoints will be analysed using appropriate descriptive summary measures. No formal statistical tests will be applied.
Signatory investigator	PPD
Sponsor	LEO Pharma A/S, Industriparken 55, DK 2750 Ballerup, Denmark

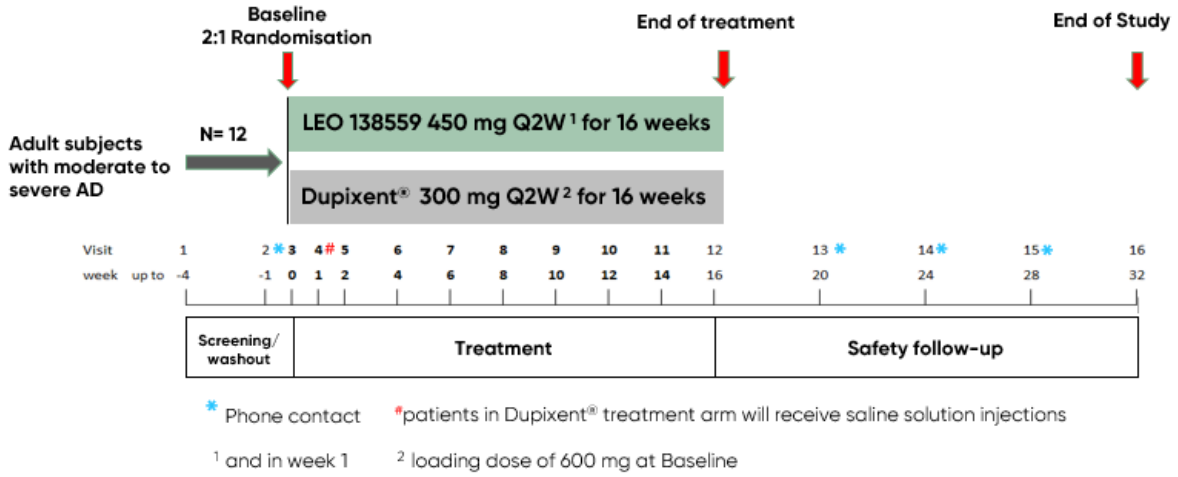
2 Trial identification

EudraCT number: 2021-006211-28

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

3 Schematic of trial design

Panel 1: Trial design



Screening period of up to 4 weeks (weeks -4 to 0) including a washout phase of 7 days (week -1 to 0). Subjects must stop treatment with TCS, TCI, topical PDE-4 inhibitors, or other topical prescription treatments 1 week prior to baseline. Washout periods for systemic treatments have to be checked at the screening visit. All subjects must use an emollient twice daily (or more frequently, if needed) for at least 7 days before day 1 (baseline) and throughout the treatment period (until week 16).

In addition to the Q2W dosing schedule during the treatment phase, subjects randomised to LEO 138559 treatment group will receive a dose of LEO 138559 at visit 4 (week 1), whereas subjects in the comparator treatment group will receive saline injections for blinding purposes.

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

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

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

	Screening[a]	Washout phone call[a]	Baseline/ Start of treatment	Treatment: Primary endpoint visit[b]								End of treatment[c]	SFU phone calls	SFU site visit End of trial visit[c]	Early termination[e]	Unscheduled. visit[f]	References (protocol section)
Visit	**1**	**2[a]**	**3**	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**Up to -28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Medical history	X		(X)[h]														11.2.2
Hepatitis B, C, HIV	X																11.4.5
Tuberculosis (*Mycobacterium tuberculosis* IFN-γ release assay)[i]	X																11.4.5
Serum pregnancy test (females only)[j]	X																11.4.5
Randomisation and treatments																	
Randomisation[k]			X														9.3.1
IMP administration at the trial site[k]			X	X	X	X	X	X	X	X	X					(X)	9.2

	Screening[a)]	Washout phone call[a)]	Baseline/ Start of treatment	Treatment: Primary endpoint visit[b)]								End of treatment[c)]	SFU phone calls	SFU site visit End of trial visit[c)]	Early termination[e)]	Unscheduled. visit[f)]	References (protocol section)
Visit	**1**	**2[a)]**	**3**	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**Up to -28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Treatment[k)] compliance at the trial site			X	X	X	X	X	X	X	X	X					(X)	9.2
Drug accountability[k)]			X	X	X	X	X	X	X	X	X					(X)	9.8.3
Background treatment (emollients)[l)]		At least twice daily															9.4
Concomitant medications/ concurrent procedures[m)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	9.6
Subject assessments (Paper Diary)																	
Paper Diary hand-out / training	X																11.7.1.1

	Screening[a)]	Washout phone call[a)]	Baseline/ Start of treatment	Treatment: Primary endpoint visit[b)]								End of treatment[c)]	SFU phone calls	SFU site visit End of trial visit[c)]	Early termination[e)]	Unscheduled. visit[f)]	References (protocol section)
Visit	**1**	**2[a)]**	**3**	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**Up to -28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Diary check by site staff/collection of completed pages			X	X	X	X	X	X	X	X	X	X	X	X	(X)		
Return of Paper Diary														X	(X)		
Investigator assessments of efficacy																	
EASI	X		X	X	X	X	X	X		X		X			(X)	(X)	11.3.3
vIGA-AD	X		X	X	X	X	X	X		X		X			(X)	(X)	11.3.1
BSA involvement	X		X	X	X	X	X	X		X		X			(X)	(X)	11.3.2
Subject assessments of efficacy																	
Worst Daily Pruritus NRS[n)]		Daily															11.7.1.2

	Screening[a)]	Washout phone call[a)]	Baseline/ Start of treatment	Treatment: Primary endpoint visit[b)]								End of treatment[c)]	SFU phone calls	SFU site visit End of trial visit[c)]	Early termination[e)]	Unscheduled. visit[f)]	References (protocol section)
Visit	**1**	**2[a)]**	**3**	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**Up to -28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Investigator assessments of safety																	
Vital signs[o)]	X		X	X	X	X	X	X	X	X	X	X		X	(X)	(X)	11.4.1
Physical examination	X		X			X		X		X		X		X	(X)	(X)	11.4.2
Weight	X											X		X	(X)	(X)	11.4.3
ECG[p)]	X		X			X		X		X		X		X	(X)	(X)	11.4.4
Clinical chemistry, haematology (central laboratory)	X		X		X	X		X		X		X		X	(X)	(X)	11.4.5.1
Urinalysis[q)]	X		X			X		X		X		X		X	(X)	(X)	11.4.5.1
Urine pregnancy test (females only)[j)]			X			X		X		X		X		X	(X)	(X)	11.4.5.1
ADA			X			X		X		X		X		X	(X)	(X)	11.4.6

	Screening[a)]	Washout phone call[a)]	Baseline/ Start of treatment	Treatment: Primary endpoint visit[b)]								End of treatment[c)]	SFU phone calls	SFU site visit End of trial visit[c)]	Early termination[e)]	Unscheduled. visit[f)]	References (protocol section)
Visit	**1**	**2[a)]**	**3**	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**Up to -28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	13.2
Pharmacokinetic assessment																	
PK blood samples			X	X		X		X		X		X		X	(X)	(X)	11.5.1
Pharmacodynamic assessments																	
Blood biomarkers (PD serum sample)			X	X		X						X			(X)	(X)	11.6.2
Skin biopsies[r)]			X	X		X						X[r)]			(X)	(X)	11.6.3
Skin tape strips			X	X		X						X			(X)	(X)	11.6.4

	Screening[a]	Washout phone call[a]	Baseline/ Start of treatment	Treatment: Primary endpoint visit[b]								End of treatment[c]	SFU phone calls	SFU site visit End of trial visit[c]	Early termination[e]	Unscheduled. visit[f]	References (protocol section)
Visit	**1**	**2[a]**	**3**	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13, 14, 15**	**16**			
Week	**-4**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20, 24, 28**	**32**			
Day	**Up to -28**	**-7**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141, 169, 197**	**225**			
Visit window (days)	**NA**	**NA**	**NA**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
End of treatment/trial																	
End-of-treatment form												X			X		10.3
End-of-trial form														X	X		

a) Screening will be performed up to 4 weeks before the baseline visit. If the screening visit is performed close to the beginning of the washout period, no additional washout phone call is necessary, at the discretion of the investigator.

b) Subjects who permanently discontinue IMP treatment prior to week 4 will be asked to return to the trial site for a primary endpoint (nominal week 4) visit.

c) An end-of-treatment form must be completed in the eCRF for all randomised subjects.

d) An end-of-trial form must be completed in the eCRF for all randomised subjects.

e) Subjects who permanently discontinue IMP prior to week 16 and subjects who withdraw from the trial will be asked to come to an early termination visit. As an early termination visit will only be performed in case of subjects permanently discontinuing the IMP, the visit has been marked with an (X).

f) Unscheduled visit(s) between planned visits may be added to the subject's visit schedule if judged necessary by the investigator, e.g. due to an AE, a significant change in disease state, or difficulty complying with the clinical trial protocol requirements. At an unscheduled visit, the investigator should at least collect AEs

data. Other assessments/procedures to be conducted at an unscheduled visit will be at the discretion of the investigator. As unscheduled visits will only be performed if judged necessary by the investigator, the assessments/procedures have been marked with an (X).

g) The informed consent form must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations and washout of disallowed medications.
h) In case medical history is incomplete at the screening visit because prior and concomitant diseases were not communicated by patient before or e.g. in case of abnormal lab values from screening assessments, missing data will be documented at week 0 (baseline).
i) Mycobacterium tuberculosis IFN-γ release assay (or a PPD test if it is a requirement from the local health authorities).
j) For women of childbearing potential
k) Preparation, administration and handling of IMPs will only be performed by unblinded site staff
l) All subjects must use an emollient twice daily (or more frequently, if needed) for at least 7 days before day 1 (baseline) and throughout the treatment period (until week 16).
m) Relevant concomitant medications/ concurrent procedures should be included from 3 months prior to baseline (day 1) until end of trial (week 32).
n) Completion of the Paper Diary for Worst Daily Pruritus NRS will be initiated at least 1 week prior to baseline (day 1). Compliance with the Paper Diary completion will be reviewed by the trial site staff throughout the trial. Subjects who discontinue IMP but remain in the trial will continue completing the Paper Diary until the safety follow-up visit (visit 16).
o) For the first 3 treatment visits (i.e. visits 3, 4, and 5) subjects will be monitored after IMP/saline administration for immediate drug reactions for a minimum of 1 hour with vital signs taken immediately after the injections as well as after 30 minutes (± 5 minutes) and after 1 hour (± 5 minutes), or until stable, whichever is later.
p) ECG should be recorded in triplicate for each time point and will be centrally evaluated.
q) Urinalysis is performed by a urine dipstick.
r) Photographs will be taken of the biopsy sites prior to each biopsy sampling
s) Suture removal in week 18, i.e., 2 weeks after the last biopsy can either be performed on site or alternatively at general practitioner as being most convenient for the subject.

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; BSA = body surface area; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eCRF = electronic case report form; HIV = human immunodeficiency virus; IFN-γ = interferon gamma; IMP = investigational

medicinal product; NRS = Numeric Rating Scale; PD = pharmacodynamics; PK = pharmacokinetics; PPD = purified protein derivative; Q2W = every second week; SFU = safety follow-up; vIGA-AD = validated Investigator Global Assessment Scale for Atopic Dermatitis.

5 Introduction and trial rationale

5.1 Atopic dermatitis

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

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

Topical therapies are the mainstay of treatment for AD and include moisturisers, TCS, TCI, and PDE-4 inhibitors [16]. In addition, topical JAK inhibitors (cream) are in development for the treatment of AD [17, 18] and the topical JAK inhibitor delgocitinib (ointment) has received marketing approval in Japan [19]. If disease control cannot be achieved with topical treatments, phototherapy can be considered [20]. For patients with moderate to severe AD, topical therapy and phototherapy are often insufficient or impractical, and therefore systemic therapy is indicated. Systemic non-biologic therapies include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. Cyclosporine is approved for the treatment of severe AD in multiple European countries and Japan. However, its use is limited by the risk of nephrotoxicity and therefore long-term therapy (>1-2 years) is not recommended. In addition, azathioprine, methotrexate, and mycophenolate mofetil have demonstrated varying levels of efficacy [21, 22] and are used off-label [23]. In 2017, the first biologic was approved for the treatment of moderate to severe AD (dupilumab, anti-IL4Ra mAb) and there are several targeted biologic therapies in development for AD including lebrikizumab and nemolizumab [24-26], as well as oral JAK inhibitors [27-29] . Of note, tralokinumab and baricitinib were

recently approved by the European Medicines Agency (EMA) for the treatment of moderate to severe AD [30], however, their position in the treatment paradigm is not yet fully understood [31].

Despite promising efficacy with dupilumab, approximately 60% of patients with AD do not achieve clinical remission (i.e. IGA 0/1, clear/almost clear). Therefore, there is a remaining unmet need to develop new therapies with improved efficacy. Further, it is increasingly recognised that AD is a phenotypically and molecularly heterogenous disease that may require differentiated and/or combined therapeutic approaches in order to adequately address the needs of patients with moderate to severe AD [32, 33].

5.2 Experience with investigational medicinal product

As LEO 138559 is still at an early stage of development only non-clinical and limited clinical data are available.

Nonclinical data

LEO 138559, originally known as ARGX-112 (clone 230C9), is a humanised IgG1 mAb with high affinity for the IL-22R1 chain of the IL-22R, thereby blocking the binding of the ligand, dimerisation of IL-22R1 with IL-10R2, and downstream signaling via JAK1-STAT3 [34]. Given the binding of LEO 138559 to IL-22R1, it is hypothesised to prevent not only the effects of IL-22 but also the effect of IL-20 and IL-24 on the IL22/24 Type II receptor (IL-20R2/IL-22R1 dimer).

Further, LEO 138559 does not bind to IL-22BP, an endogenous negative regulator of IL-22, and thereby leaves IL-22BP free to further inhibit IL-22 activity [35].

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

Toxicology

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

The LEO 138559 nonclinical data indicated a toxicity profile that is amenable to clinical monitoring, is of low concern for human risk, and provides an approximate 16-fold margin of

exposure between the observed NOAELs and the exposure at steady state for 450 mg Q2W dosing (planned dosing regimen in LP0145-2274).

The nonclinical results did not indicate a need to perform specific clinical trials (typically conducted for small molecule drugs) investigating effects on QT prolongation, implication of hepatic or renal impairment and, cytochrome P450 induction/inhibition potential.

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

From the mode of action (MoA), target expression, class effects of other biologics, and literature review, potential risks have been identified which are included in the investigator's brochure (Section 7.3.2) [36].

A detailed overview of nonclinical data on LEO 138559 is available in the current investigator's brochure [36].

Clinical data
One first-in-human (FiH) clinical trial with LEO 138559 was completed (LP0145-1315) and further trials (PK and proof of concept) with LEO 138559 are ongoing.

The FiH trial was a randomised, double-blind, placebo-controlled, multi-centre trial to evaluate the safety, tolerability, PK, and PD of LEO 138559 in healthy volunteers (HV) and subjects with moderate to severe AD. The trial contained a single-ascending dose (SAD) and multiple-ascending dose (MAD) part with overall 51 subjects. SAD were administered intravenously (IV) and subcutaneously (SC) in healthy volunteers (HV). MAD were administered SC in HV and patients with AD. In patients with AD (data from 8 patients were available), a reduction in disease severity based on individual EASI scores was observed for LEO 138559 compared with placebo.

No fatal events, no SAEs, and no severe AEs were reported during the trial. No AE patterns giving rise to any concerns have been reported from the 35 subjects who received LEO 138559. 19 HV were exposed to single doses of LEO 138559 (IV in 11 HV, and SC in 8 HV), and 12 patients with AD and 4 HV were exposed to multiple SC doses of LEO 138559.

Among a total of 17 adverse events considered as possibly or probably related to the treatment reported in 8 subjects either receiving single or multiple doses of LEO 138559, the most frequently reported adverse events were infections and infestations observed in 6 of 35 subjects exposed to LEO 138559 and considered mild to moderate in severity at most.

Furthermore, nervous system disorders were reported for a total of 3 subjects, 2 of them having a single episode of headache and a 3rd subject reported to suffer from dizziness. In addition, 2 subjects developed skin and subcutaneous disorders. All other adverse events were reported only once without any clustering or trends for a special type of events.

Overall, there were no clinically relevant treatment effects on vital signs and clinical laboratory parameters. No severe AEs were reported. No risks for humans have been identified at the dose levels of up to 450 mg LEO 138559 dosed weekly (the selected dose for biweekly dosing in the present trial) tested to date.

Pharmacokinetics
Based on the human PK data from the FiH trial, the PK of LEO 138559 is as expected for a mAb (IgG1) directed toward a membrane-bound target, and the target-mediated drug disposition (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 7.5 days. After multiple dosing, the elimination half-life was observed to be between 21–25 days. At and above the exposure level relevant for clinical testing (150 mg Q2W), the elimination is dominated by linear clearance and close to dose-proportionality is expected at steady state. The exposure at steady state following administration of 450 mg Q2W is expected to result in lower exposure than 450 mg every week for 5 weeks (the highest dose in the LP0145-1315 trial).

A detailed overview of clinical data on LEO 138559 is available in the current investigator's brochure [36].

5.3 Trial rationale

There remains an unmet need for effective treatment options in patients with moderate to severe AD. Building on the knowledge of increased IL-22 expression in AD, it is hypothesized that inhibition of the IL-22 pathway via LEO 138559 may be an effective treatment in patients with moderate to severe AD. The primary goal of this exploratory mechanistic trial will be to evaluate changes in biomarkers in skin and blood in atopic dermatitis patients after treatment either with LEO 138599 or with comparator.

As comparator dupilumab (Dupixent®) will be used, a biologic treatment approved for the treatment of moderate-to-severe AD. This monoclonal IgG4 antibody selectively inhibits IL-4Rα.

5.4 Ethical considerations

This trial will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki [37] and ICH GCP [38] and in compliance with the approved protocol and applicable regulatory requirements.

The trial design is considered scientifically justified and to adhere to ethical standards ensuring the rights, safety, and well-being of the subjects. The efficacy and safety of LEO 138559 will be evaluated in adults with moderate to severe AD who may benefit from treatment with LEO 138559. Appropriate measures will be taken to protect the subject from potential risks related to treatment with LEO 138559 and to closely monitor the subject as explained in Section 5.5 below.

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

Women who are pregnant (or trying to become pregnant) and women who are breastfeeding will not be included in the trial. Women of childbearing potential must agree to use a highly effective form of contraception to prevent pregnancy during the trial. In addition, pregnancy tests for all women of childbearing potential will frequently be conducted during the trial to detect any pregnancies.

Subjects not able to provide informed consent will not be included in the trial.

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

5.5 Benefit/risk assessment

LEO 138559

No risks have been observed in nonclinical studies or clinical trials with LEO 138559.

According to the results from the FiH (LP0145-1315), single IV doses up to 75 mg, single SC doses up to 300 mg, and multiple SC doses up to 450 mg LEO 138559 are considered safe and well tolerated. No severe or serious AEs were reported in this trial.

The following are considered important potential risks for LEO 138559 based on mechanism of action and class effects of other biologics.

IL-22 has been shown to mediate cutaneous and mucosal host defence in the skin, lung, and intestine and induce expression of epithelial antimicrobial peptides. Therefore, when blocking IL-22R, there is a potential for increased risk of infection. However, based on the data reported in subjects with AD treated with the monoclonal antibody targeting IL-22 (fezakinumab) and the available data from LEO138559, no increased risk of infections has been observed by blocking the IL- 22 pathway.

IL-22 is known to play a role in tissue regeneration and wound healing and blocking IL-22R could potentially delay skin, lung, intestine, and pancreas healing. The risk is considered low as many growth factors and cytokines have overlapping roles for tissue regeneration and wound healing.

Immunogenicity is a class effect of mAbs, though the risk of immunogenicity of LEO 138559 is predicted to be lower than current biologics as predicted by the in silico Epibase scanning system [39].

Anaphylaxis and serious allergic reactions have been observed after the administration of mAbs and other foreign proteins. In addition, AD subjects are at an increased risk of hypersensitivity reactions.

However, in the FiH trial, no trends for impaired wound healing, no anaphylaxis or serious allergic reactions were observed.

The FiH trial revealed promising efficacy results in AD patients for the 300 mg and 450 mg treatment groups. Treatment- and dose-related reductions in mean EASI and IGA scores were observed. Reductions from baseline in EASI score ≥90% occurred in 3 out of 4 subjects following administration of 450 mg LEO 138559.

Dupixent®

As comparator dupilumab (Dupixent®) was chosen, a systemic targeted immunomodulatory agent approved for the treatment of moderate-to-severe AD since 2017. Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced

responses, including the release of proinflammatory cytokines, chemokines and IgE and modulated the Type 2 pathway.

Dupixent® will be used in this trial in a dosing scheme as per approved label in Austria.

Side effects are injection site reactions (includes erythema, oedema, pruritus, pain, and swelling), conjunctivitis, arthralgia, oral herpes, and eosinophilia. Rare cases of serum sickness, serum sickness-like reaction, anaphylactic reaction, and ulcerative keratitis have been reported as described in the summary of product characteristics (SmPC) for Dupixent®.

Trial-related procedures

Blood sampling presents the same low risk as normally associated with this procedure (i.e. infection, bleeding into the surrounding tissue, and, very rarely, inflammation of the vein, or formation of blood clots). Blood sampling will only be conducted by qualified medical personnel.

Subjects may experience discomfort associated with the collection of the skin biopsy samples. To minimize discomfort, the subject will receive an injection of a local anesthetic to numb the area where the biopsy will be taken. Subjects who have previously had reactions to an anesthetic medication will not be included in this trial. Complications of skin biopsies may include bleeding, infection, bruising and/or pain at the biopsy site. Pressure dressings and ice may be used to help alleviate these symptoms. Wound healing at the biopsy site will be checked at a subsequent visit and sutures removed as needed. The subject will be informed that they may retain small scars after the procedure.

Collection of tape strips is a non-invasive technique with no or very limited risks to the subject.

Participation in clinical trials may currently be associated with increased risks and challenges due to the COVID-19 pandemic caused by SARS-CoV-2. Based on non-clinical studies, LEO 138559 is considered a mild immunomodulatory compound and its mechanism of action is not believed to present a risk of a decreased antiviral immunity in subjects infected by COVID-19. In addition, LEO 138559 is not believed to increase the susceptibility of the subject to contract COVID-19 or other infections. However, a risk of exposure to infected people cannot be excluded as the subject may enter public areas (e.g., commute to the trial site) and have human contacts (e.g., with the site staff). Therefore, risks must appropriately be assessed, and mitigation measures taken to protect the subject and site staff and to ensure the integrity of the trial data. Several exclusion criteria have been chosen to reduce the risk for

participants for infection with SARS-CoV-2 (Appendix 5: Short version and justification for eligibility criteria). Vaccination with mRNA vaccines for SARS-CoV-2 will be allowed during the trial.

Both EMA and as well as national and local health authorities in Europe have issued new guidelines aiming at providing recommendations for conduct of clinical trials during the COVID-19 pandemic [40-42]. Given the potential for the pandemic situation to relapse in relation to spread of COVID-19 in the future, special attention will be paid to protecting subjects and site staff involved in the trial against infection with SARS-CoV2.

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

Mitigation measures that are currently planned to be implemented in this clinical trial in case of an escalation of pandemic situation are detailed in a separate document ("Mitigation Measures due to COVID-19 Pandemic"), that will be part of the submission package send to the relevant Ethics Committee and the Competent Regulatory Authority for approval.

As a result of the ongoing risk evaluation, further mitigation measures may come into force, resulting in an update of the above-mentioned document. If additional mitigation measures require approval, a substantial amendment will be submitted to the relevant Ethics Committee and the Competent Regulatory Authority and will not be implemented until approved. Exceptions to this are amendments made to eliminate immediate hazards to the patients ("urgent safety measures"). In this case the relevant Ethics Committee and the Competent Regulatory Authority will be notified about changes as soon as possible considering national and local circumstances.

Conclusion

The study population consists of subjects with moderate to severe AD. Since all subjects will receive active treatment (either the investigational drug (LEO138559) or an approved drug for comparison (Dupixent®) it is likely that they will benefit from study participation. With the above provisions in place, the risks associated with participating in the trial are considered low and outweighed by the benefit of a potential future SC treatment option for AD. The current benefit-risk profile is therefore deemed in favour of conducting the present trial.

6 Trial objectives and endpoints

Trial objectives and endpoints are presented in Panel 3. Further details about the statistical analyses of the endpoints are presented in Section 14.3.

Panel 3: Objectives and endpoints

Objectives	Endpoints
Primary objective	
To investigate the molecular signature changes in subjects with moderate to severe atopic dermatitis (AD) following treatment with LEO 138559 and Dupixent®	**Primary endpoint** • Change in biomarkers typically associated with atopic dermatitis in lesional skin biopsies from baseline to week 4.
Secondary objective	
To evaluate the safety of LEO 138559 in subjects with moderate to severe AD	**Secondary endpoint** *Secondary endpoint* • Number of treatment-emergent adverse events from baseline to week 16 per subject. *Exploratory endpoint (ADA)* • Having a positive ADA response at weeks 0, 4, 8, 12, 16, 32, assessed separately.
Exploratory objectives	
To evaluate the efficacy of LEO 138559 and Dupixent® in subjects with moderate to severe AD	**Exploratory endpoints (efficacy)** • Change in EASI score from baseline to week 1, 2, 4, 6, 8, 12, and 16. • Having a decrease in EASI of at least 50% (EASI 50) from baseline to week 1, 2, 4, 6, 8, 12, and 16, assessed separately. • Having a decrease in EASI of at least 75% (EASI 75) from baseline to week 1, 2, 4, 6, 8, 12, and 16, assessed separately. • Having a decrease in EASI of at least 90% (EASI 90) from baseline to week 1, 2, 4, 6, 8, 12, and 16, assessed separately. • Having vIGA-AD score of 0 (clear) or 1 (almost clear) at week 1, 2, 4, 6, 8, 12, and 16, assessed separately. • Change in Worst Daily Pruritus NRS (weekly average) from baseline to weeks 1, 2, 4, 6, 8, 12, and 16.Change in EASI score from baseline to week 1, 2, 4, 6, 8, 12, and 16.

Objectives	Endpoints
	• Having a decrease in EASI of at least 50% (EASI 50) from baseline to week 1, 2, 4, 6, 8, 12, and 16, assessed separately. • Having a decrease in EASI of at least 75% (EASI 75) from baseline to week 1, 2, 4, 6, 8, 12, and 16, assessed separately. • Having a decrease in EASI of at least 90% (EASI 90) from baseline to week 1, 2, 4, 6, 8, 12, and 16, assessed separately. • Having vIGA-AD score of 0 (clear) or 1 (almost clear) at week 1, 2, 4, 6, 8, 12, and 16, assessed separately. • Change in Worst Daily Pruritus NRS (weekly average) from baseline to weeks 1, 2, 4, 6, 8, 12, and 16.
To evaluate the pharmacokinetics of LEO 138559 in subjects with moderate to severe AD	**Exploratory endpoint (pharmacokinetics)** • Serum concentration of LEO 138559 at weeks 0, 1, 4, 8, 12, 16, and 32.
To evaluate the effect of treatment with LEO 138559 or Dupixent® on disease biomarkers in subjects with moderate to severe AD	**Exploratory endpoints (pharmacodynamics)** • Change in expression of AD disease biomarkers in skin biopsies from baseline to week 1 and 16. • Change in expression of additional AD disease biomarkers in serum from baseline to week 1, 4, and 16. • Change in expression of additional AD disease biomarkers in skin tape strips from baseline to week 1, 4, and 16.

Abbreviations: AD = atopic dermatitis; EASI = Eczema Area and Severity Index; EASI 50/75/90 = at least 50%/75%/90% decrease in EASI score; NRS = numeric rating scale; vIGA-AD = validated Investigator Global Assessment for AD

7 Trial design

7.1 Overall trial design

This is a randomised, double-blinded, active comparator-controlled, 16-week, single-site, exploratory, mechanistic trial to assess the effect of LEO 138559 on the molecular signature and safety in adults with moderate to severe AD. A schematic overview of the trial design is presented in Panel 1.

The trial will consist of:

- A screening period of up to 4 weeks (weeks -4 to 0) including an applicable washout period of 7 days (week -1 to 0).
- A treatment period of 16 weeks (weeks 1 to 16).
- A follow-up period of 16 weeks (weeks 17 to 32).

On day 1 (visit 3) subjects will be randomised to either LEO 138559 or the comparator. The primary endpoint will be assessed at week 4. The final safety assessments will be conducted at week 16 (end of treatment).

The subject's visit schedule and the procedures and assessments to be conducted at each visit are presented in Section 4. If necessary, an unscheduled visit can be performed at any time and for any reason at the discretion of the investigator.

Screening period (up to 4 weeks prior to the baseline visit [day 1])
Subjects' eligibility to enter the clinical trial will be evaluated at a screening visit (visit 1) including the check of washout periods for systemic treatments. This visit will be performed up to 4 weeks before the baseline visit (visit 3).

Subjects will be reminded with a phone call (visit 2) at the beginning of the washout period (7 days before the baseline visit [visit 3, day1]), to stop any treatment with TCS, TCI, PDE-4 inhibitors, or other topical prescription AD treatments, and start application of an emollient to all affected areas of the skin twice daily (or more frequently, if needed). The daily application of the emollient should continue throughout the treatment period. At the screening visit (visit 1), the subjects will be provided with a diary and will be instructed to record the Worst Daily Pruritus NRS and the application of the above-mentioned daily application of emollients. Completion of the diary will be initiated at the latest 1 week prior to the baseline visit (visit 3, day 1).

All procedures will be performed as specified in Panel 2.

Treatment period (week 1 to week 16)
After confirmation of the eligibility at the visit 3 (day 1) the assessments as specified in Panel 2 and Panel 6 (sequence of assessments) will be performed and the subjects will be randomised. LEO 138559 or comparator injections will be administered at the trial site by site staff Q2W for 16 weeks (Section Administration of investigational medicinal products9.2). Only site staff responsible for handling of IMPs and preparation and administration of the injections will be unblinded and will not be involved in the efficacy and safety assessments during the trial. In addition to the Q2W dosing schedule, the LEO 138559 treatment group will receive an additional dose of their allocated treatment at visit 4 (week 1). Subjects randomised in the comparator treatment group will receive the same number of injections as subjects in the LEO 138559 treatment group to keep the blinding (as further detailed in a separate trial product handling manual and the blinding plan). The additional injections will include saline solution. During the treatment period, the subject will be asked to continue applying the emollient twice daily (or more frequently, if needed). The subject will be asked to visit the clinic for assessments and procedures for 9 visits (until week 16) as specified in Panel 2. Final dosing will be administered at week 14, regardless of AD improvement.

Safety follow-up period (week 17 to week 32)
In the safety follow-up period, the subject will not receive any treatment with LEO 138559 or comparator injections. The safety of the subject will further be assessed at 3 safety follow-up phone calls (weeks 20, 24, and 28) and at a final safety follow-up visit at week 32. Topical treatment for AD will be permissible during the safety follow-up period. At the end of trial visit the diary will be collected and assessments will be conducted as specified in Panel 2.

Subjects who require treatment with other biologics will prematurely discontinue the trial.

Subjects who discontinue the trial early should be requested to return for an early termination / end of trial visit (see also Section 10.3) at the time of the decision to withdraw from the study.

7.2 Number of subjects needed

This trial will be conducted at one site in Austria. Approximately 12 subjects will be randomised in a 2:1 ratio to LEO 138559 450 mg Q2W (8 subjects) and comparator 300 mg Q2W (4 subjects) to be able to achieve 12 subjects evaluable for the primary endpoint i.e., for whom a lesional biopsy is available at baseline and week 4.

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

7.3 End-of-trial definition

A subject is considered to have completed the trial if they have completed all periods of the trial including the safety follow-up visit at week 32 (see Section 11.8 for data to be recorded on the end-of-trial form).

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

Final collection of data for the primary endpoint occurs at week 4. Therefore, the primary completion date is defined as the date of last week 4 visit for the last subject in the trial.

8 Trial population

8.1 Subject eligibility

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

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

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

8.2 Inclusion criteria

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

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures.
2. 18 – 64 years old (both included) at screening.
3. Diagnosis of AD [as defined by the AAD Consensus Criteria [43] that has been present for ≥1 year prior to screening.
4. Subjects who have a recent history (within 6 months before screening) of inadequate response to treatment with topical medication, or for whom topical treatments are otherwise medically inadvisable.
   - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to higher potency (±TCI as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super potent TCS), whichever is shorter.
   - Subjects with documented systemic treatment or phototherapy for AD in the past 6 months are considered as inadequate responders to topical treatment and are potentially eligible for trial inclusion after appropriate washout.
5. EASI score ≥12 at screening and ≥16 at baseline.
6. vIGA-AD score ≥3 at screening and baseline.
7. Body surface area (BSA) of AD involvement ≥10% at screening and baseline.

8. Worst Daily Pruritus NRS (weekly average) of ≥3 points at baseline.
   NOTE: The baseline weekly average will be calculated from daily assessments of itch severity during the 7 days immediately preceding randomisation. A minimum of 4 daily itch scores out of the 7 days is required to calculate the baseline average score. Only for subjects who do not have at least 4 daily itch scores reported during the 7 days immediately preceding the planned randomisation date, randomisation can be postponed until the requirement of 4 daily entries is met, but without exceeding the 28-day maximum duration for screening.
9. Subject agrees to apply an emollient twice daily (or more frequently, if needed) to AD lesional and non-lesional skin for at least 7 days before baseline.
10. A woman of childbearing potential* must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline.
11. A woman of childbearing potential* must use a highly effective** form of birth control throughout the trial and at least for 18 weeks after last administration of IMP.

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

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

8.3 Exclusion criteria

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

1. Treatment with systemic immunosuppressive/immunomodulating medication (excluding systemic antihistamines if taken at stable dose already before baseline), e.g., JAK inhibitors, immunoglobulin/blood products within 2 weeks or 5 half-lives prior to baseline, whichever is longer.

2. Treatment with systemic corticosteroids within 4 weeks prior to baseline
   NOTE: Inhaled or intranasal steroids equivalent to doses including and up to 500 µg beclometasone (or equivalent) daily is allowed.
3. Intake of nonsteroidal anti-inflammatory drugs (NSAIDs) within 1 week prior to baseline.
   NOTE: Intake of paracetamol will be allowed.
4. Treatment with biologics within 5 half-lives (if known) or 16 weeks prior to baseline, whichever is longer.
5. Allergen immunotherapy within 4 weeks prior to baseline.
6. Treatment with TCS, TCI, topical PDE-4 inhibitor, or other topical prescription treatments (i.e., medications or prescription emollients/moisturisers (other than the ones allowed during treatment period) used for the treatment of AD) within 1 week prior to baseline.
   NOTE: Subject may be rescreened (once) if failed for this criterion (see Section 8.4).
7. Use of tanning beds or phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]) within 4 weeks prior to baseline.
8. Treatment with a live (attenuated) vaccine within 12 weeks prior to baseline.
9. Active dermatologic condition that could confound the diagnosis of AD or interfere with assessment of the treatment.
10. History of malignancy within 5 years prior to baseline, apart from non-metastatic basal cell carcinoma, squamous cell carcinoma of the skin, or cervical carcinoma in-situ, considered cured by the standard of care.
11. Clinically significant active chronic or acute infection requiring systemic treatment within 4 weeks prior to baseline that may compromise the safety of the subject.
    NOTE: Subject may be rescreened (once) after infection resolves (see Section 8.4).
12. Skin infection within 1 week prior to the baseline visit.
    NOTE: Subject may be rescreened (once) after infection resolves (see Section 8.4).
13. Current or recent (within 2 years prior to baseline) gastrointestinal ulcers.
14. History of any of the following: anaphylaxis, immune complex disease, pancreatic disease, inflammatory bowel disease or known or suspected history of immunosuppressive disorder.

15. Known or suspected hypersensitivity to any component(s) of the IMPs.
16. Known or suspected hypersensitivity to local anesthetics.
17. Presence of hepatitis B or C infection at screening. These are defined as: 1) Positive hepatitis C Ab, or 2) Positive HBsAg, or 3) Negative anti-HBs Ab AND positive anti-HBc Ab.
18. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.
19. Subject has a positive or indeterminate *Mycobacterium tuberculosis* IFN-γ release assay test or a positive purified protein derivative (PPD) test at screening.
    NOTE: The PPD test is only accepted if it is a requirement from local health authorities.
20. Current diagnosis of diabetes.
21. Clinically significant abnormalities detected on vital signs or ECG (apart from 1st degree atrioventricular (AV) block that is allowed).
22. Serious heart conditions (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and/or pulmonary hypertension).
23. Chronic lung diseases (e.g., chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and/or cystic fibrosis).
24. Acute asthma, acute bronchospasm, moderate to severe asthma [as defined by GINA guidelines [44]].
25. Obesity (BMI ≥35).
26. Subject has laboratory abnormalities that, in the opinion of the investigator, will prevent the subject from completing the trial or interfere with the analysis of results.
27. Subject is pregnant or lactating.
28. Subject has a history of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
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. Any disorder* at screening and/or baseline, which is not stable in the opinion of the investigator, and could:
    a. Affect the safety of the subject throughout the trial.

b. Influence the findings of the trial.

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

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

31. Any significant abnormal finding* at baseline and/or screening which may in the opinion of the investigator:

    a. Put the subject at risk because of their participation in the trial.

    b. Influence the results of the trial.

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

    *Examples include clinically significant abnormal vital sign, physical examination, ECG, and laboratory result.

32. 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 baseline, whichever is longer.

33. Current participation in any other interventional clinical trial.

34. Previously randomised in this clinical trial.

35. Subjects who are legally institutionalised.

8.4 Screening and screening failures

Subject identification number

Trial participation begins once written informed consent is obtained. Refer to Appendix 3B for details on the informed consent process. Once informed consent is obtained, subjects will be assigned to ascending subject identification numbers (subject ID) in the order of their appearance at screening and the screening evaluations to assess eligibility criteria may begin. The subject ID will be automatically generated by the eCRF system. The generation and composition of the subject ID will be described in the Completion Guide for the eCRF. The date of first screening activity could be on the same day or a later date than the informed consent was signed. The subject ID will be used to identify the subject during the screening process and throughout trial participation, if applicable. Subjects who have given written informed consent to participate in the trial and who have been assigned a subject ID are considered 'screened' subjects.

The investigator will maintain a log of all consented subjects at the trial site (subject identification list) including subjects who are not randomised in the trial/ treatment assigned.

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 date of screening and the status (screening failure or randomised) should also be documented. The log must not be copied or retained by LEO Pharma. All subjects who signed the informed consent form must be entered into the eCRF.

Screening failures

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

- Date of informed consent(s).
- Demographics (age, sex, ethnicity, race).
- Reason for screen failure.
    - Failure to meet eligibility criteria.
    - Lost to follow-up.
    - Withdrawal by subject.
    - Other.
- Date of screen failure.
- Re-screening of the subject, if applicable
- Any adverse events (AEs) and serious AEs (SAEs).

In case of any SAEs, these must be followed up as described in Section 13.

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

- if the reason for screening failure is administrative and not due to the subject not meeting the eligibility criteria (e.g., delayed test results),
- an infection resolves after initially not having met exclusion criteria no. 11 (active chronic or acute infection requiring systemic treatment) or no. 12 (skin infection),
- if the subject failed exclusion criterion no. 6 (treatment with TCS, TCI, or topical PDE-4 inhibitor, or other topical prescription treatments within 7 days 1 week prior to baseline).

Rescreening may be permitted once and 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. Rescreened subjects will get a new subject ID.

9 Treatments

9.1 Trial product description

In this trial the test drug LEO 138559 and the comparator Dupixent® will be used.
LEO 138559 is presented as a lyophilised powder for reconstitution and administration as injection. The comparator will be used as commercially available product and is presented as pre-filled syringe for injection.

Refer to Panel 4 for further details.

Panel 4: Identification of investigational medicinal products

Investigational medicinal product	Dosage form	Active ingredients and concentration	Pack sizes	Manufacturer responsible for batch release
LEO 138559	Lyophilised powder for reconstitution (using 1.0 mL sterilised water) adding up to a volume of 1.2 mL/vial to achieve a solution for SC injection	LEO 138559, 150 mg/mL (following reconstitution)	1 vial for 150 mg/mL (following reconstitution)	LEO Pharma
Dupixent®	Pre-filled syringe with 300 mg in 2 ml solution for SC injection	Dupilumab, 150 mg/mL.	300 mg pre-filled syringe	Sanofi-Aventis Groupe

Note: To ensure that 1.0 mL can be withdrawn by a syringe, there will be a small overfill in the test drug vial after reconstitution, of approximately 0.2 mL per vial.
Abbreviation: SC = subcutaneous(ly).

9.2 Administration of investigational medicinal products

The IMP will be administered to the subject according to the schedule of trial procedures (Section 4). The first day of dosing is considered day 1. For blinding purposes all subjects will receive the same number of injections i.e., subjects in the comparator treatment group will receive injections with saline solution in addition to their injection of Dupixent®. Sterile water for reconstitution of LEO 138559 and saline solution for additional injections will be taken from the stock at the trial site. Details on the handling of the IMP and related procedures to maintain blinding will be described separately (trial product handling manual and blinding plan).

To further ensure blinding of subjects, subjects will be asked to cover their eyes (e.g., with a sleep mask or a loose bandage) prior to the administration of the IMP.

IMP will be administered by subcutaneous injections every other week (Q2W) during the treatment period. While subjects in the LEO 138559 treatment group will receive an additional dose in week 1 (visit 4), subjects in the comparator group will receive injections with saline solution at visit 4.

During the treatment period, final dosing will be administered at week 14 and the clinical assessment will occur at week 16. IMP administration will continue until week 14, regardless of AD improvement.

IMPs will be prepared and administered at the site by qualified, unblinded site staff as the two IMPs are distinct in appearance and dosing scheme (for details about blinding see section 9.3.2). IMP (or saline solution) will be injected SC in the upper legs (thighs), stomach area (abdomen, except in an area of 5 cm around the navel) or in the upper, outer arm but should not be given into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by AD. The anatomical location of the injection, and if it was on the right or left side, must be recorded in the source documents at each treatment visit and recorded in the eCRF.

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

If any issues with the IMPs (e.g., damaged kit or vial/syringe) or a malfunction during administration should arise, please refer to the trial product handling manual supplied by LEO Pharma.

LEO 138559 administration:

Each subject in the LEO 138559 treatment group will receive 3 SC injections (each 1.0 mL) of 150 mg LEO 138559 to receive a total dose of 450 mg LEO 138559. In addition to the Q2W dosing schedule, LEO 138559 treatment group will receive an additional dose at visit 4 (week 1). Further details on preparation and administration of LEO 138559 will be provided in an instruction for use and trial product handling manual. IMP administration must be carried out according to these instructions.

Comparator (Dupixent®) administration:

Dupixent® is approved for the treatment of moderate to severe AD in adults in Austria and will be administered according to the prescribing information. On day 1 each subject in the comparator treatment group will receive 2 SC injections (each 2.0 mL) of the comparator 300 mg Dupixent® to receive an initial dose of 600 mg dupilumab. On subsequent dosing days the comparator will be administered by site staff as 1 SC injection of 2 mL (300 mg dupilumab). For blinding purposes, subjects will receive 1 additional SC injection with 1 mL saline solution on day 1 and 3 SC injections with saline solution (each 1.0 mL) at visit 4. On subsequent dosing days subjects will receive 2 SC injections with saline solution (each 1.0 mL) in addition to the injection of the comparator.

After IMP administration

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

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

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

Conditions requiring IMP administration rescheduling

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

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

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

There are no specific treatment recommendations in relation to overdose of the IMP. The investigator will monitor the subject for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately according to clinical judgement to treat any overdose if necessary. For reporting of overdose, see Section 13.6.1.

9.3 Treatment assignment and blinding

9.3.1 Treatment assignment

Treatment assignment will be pre-planned according to a computer-generated randomisation schedule. This **randomisation schedule** randomly allocates subjects who have been found to comply with all the inclusion criteria and not to violate any of the exclusion criteria on day 1 (visit 3) in a 2:1 ratio to one of the two treatments, LEO 138559 or comparator. Randomisation envelopes will be provided to the site. The randomisation number has to be documented in the CRF.

9.3.2 Blinding

This is a double-blinded trial in which LEO 138559 and comparator are visually distinct from each other and have a different dosing scheme. Neither the subject nor any of the investigators or LEO Pharma staff (except unblinded CRAs) who are involved in the clinical evaluation and monitoring of the subjects will be aware of the treatment received. IMP and syringes will be prepared and administered by a qualified, unblinded trial site staff who will not be involved in the management of trial subjects and who will not perform any of the assessments.

Three syringes will be prepared by unblinded site staff for each subject at each dosing visit containing either LEO 138559 or, for subjects in the comparator group, Dupixent® and saline solution (to account for 3 syringes in total). Before administration of the injections, subjects will be blinded i.e., their eyes will be covered (e.g., by a sleep mask) as specified in a blinding plan, so they are not able to identify which treatment they receive.

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

The trial site will maintain a written plan (site blinding plan) that specifies which staff members are blinded or unblinded and the procedures used to maintain blinding including the measures to keep the blinding for the subjects.

9.3.3 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, health care professionals (HCPs) who are not members of the trial staff, or authorised LEO Pharma personnel.

Provisions are in place for 24-hour emergency unblinding of individual subject treatment. If emergency unblinding is required, the requesting person can directly contact the emergency unblinding CRO via a corresponding local emergency unblinding telephone number, that can be found in the Investigator Site File (ISF).

The investigator or delegated site staff will need to provide the trial ID, the subject ID and the randomisation code number of the subject to the emergency unblinding CRO who will immediately reveal the individual treatment allocation.

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

The emergency unblinding CRO will clarify that the requester requires immediate unblinding without further medical consultation.

Unblinding should only be done in case of an emergency and when it is essential for effective treatment of the subject. Most often, trial drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat the subject. The Sponsor is to be informed immediately about any unblinding event.

Documentation of any emergency unblinding by the assessor should include the date of the unblinding and the reasons that led to unblinding. It has to be reported on the blind break form filed in the Investigators site file. In addition, AEs or SAEs related to the unblinding have to be reported appropriately.

LEO Pharma Global Safety will receive a set of emergency envelopes, including the identity of the product codes for potential unblinding for regulatory purpose.

9.4 Background treatment

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

Subjects may continue using stable doses of their moisturizers if initiated before the screening visit. Subjects may not initiate treatment with prescription moisturizers or moisturizers containing additives (ceramide, hyaluronic acid, urea, filaggrin degradation products) during the screening period or during the treatment period. To ensure use of a suitable emollient, the investigator should provide guidance to the subject as to which locally available emollient to use.

The function of the emollient is to:

- Keep the subject's skin well moisturised in the absence of systemic and/or topical AD treatment(s) in the washout period (week -1 to week 0).
- Act as a complement to systemic treatment with the IMP (standard of care) and keep the subject's skin well moisturised in the treatment period (week 1 to week 16).

The subjects will document the use of the emollients in the diary. It will be recorded in the eCRF if background treatment (emollient) has been used daily; if not, a reason should be provided.

9.5 Rescue treatment

In case subjects require additional treatment for atopic dermatitis during the treatment phase, as a first step, TCS / TCIs are recommended, and administration of study drug will be continued. Should other systemic AD therapy be required (e.g., cyclosporin A, oral JAK inhibitors, oral corticosteroids), the IMP administration should be stopped, and the subject will be withdrawn from the trial. Any use of AD therapy other than the trial treatment (see also section 9.7) needs to be documented in detail in the eCRF including use of emollients (see also section 9.4.)

9.6 Concomitant medication and concurrent procedures

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

- Medication name or therapy (generic or brand name).
- Indication.
- Start and stop date of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose per administration, unit, and frequency.
- Route of administration: oral, topical, subcutaneous, transdermal, intraocular, intramuscular, respiratory (inhalation), intralesional, intraperitoneal, nasal, vaginal, rectal, intravenous, or other (if other, a specification must be provided).
  For topical treatments, the dosage form (cream, lotion, ointment, other) will also be recorded.
  For topical, SC, transdermal, intramuscular, and intralesional treatments, the location of administration including laterality will also be recorded (e.g. left upper arm).

Similarly, any concurrent procedure must also be recorded in the subject's medical record and the eCRF. The following details will be recorded:

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

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

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

The following concomitant medications are permitted from screening through safety follow-up:

- Paracetamol use (maximum 2 g/day).
- Systemic antihistamines, if taken at a stable dose before baseline
- Concomitant therapies taken for the long-term treatment of pre-existing conditions can continue during the trial provided they are in accordance with the exclusion criteria (see Section 8.3).
- Inhaled or intranasal steroids equivalent to doses including and up to 500 µg beclometasone (or equivalent) daily

9.7 Prohibited medication(s) and procedures

The medications and/or procedures listed in Panel 5 are prohibited during the trial. Details regarding prohibited medications and/or procedures prior to screening and during wash-out(s) are described in Section 8.3.

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

Medication or procedure	Prohibited from	Prohibited to
TCS, TCI or topical PDE-4 inhibitors.	7 days prior to baseline (Washout).	Week 16.
Other topical prescription medications or prescription emollients/moisturisers (other than the ones allowed during treatment period) used for the treatment of AD.	7 days prior to baseline (Washout).	Week 16.
Intake of nonsteroidal anti-inflammatory drugs (NSAIDs), except Paracetamol	7 days prior to baseline	Week 16.
Use of UVA, UVB, PUVA, other phototherapy, or tanning beds.	4 weeks prior to baseline.	Week 16.
Immunoglobulin or blood products.	4 weeks or 5 half-lives prior to baseline, whichever is longer.	Safety follow-up (week 32).
Systemic corticosteroids (excluding inhaled or intra-nasal steroids).	4 weeks prior to baseline.	Safety follow-up (week 32). If medically indicated and deemed necessary at investigator's discretion a patient may receive therapies with systemic corticosteroids during the safety follow-up.
Systemic immunosuppressive/immuno-modulating medication, (excluding systemic antihistamines if taken at a stable dose before baseline), e.g., JAK inhibitors.	2 weeks or 5 half-lives prior to baseline, whichever is longer.	Safety follow-up (week 32). If medically indicated and deemed necessary at investigator's discretion a patient may receive therapies with systemic corticosteroids during the safety follow-up.

Medication or procedure	Prohibited from	Prohibited to
Biologics	16 weeks or 5 half-lives prior to baseline, whichever is longer.	Safety follow-up (week 32). If medically indicated and deemed necessary at investigator's discretion a patient may receive therapies with systemic corticosteroids during the safety follow-up.
Allergen immunotherapy.	4 weeks prior to baseline.	Safety follow-up (week 32). If medically indicated and deemed necessary at investigator's discretion a patient may receive therapies with systemic corticosteroids during the safety follow-up.
Live (attenuated) vaccine.	12 weeks prior to baseline.	Safety follow-up (week 32).

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

In case any prohibited treatments are used during the trial, they must be recorded as concomitant medication and the sponsor's medical expert must be notified immediately if a subject receives any of these prohibited medications during the trial.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

IMPs will be packed open label in individually numbered kits.

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

The labelling of IMPs will be in accordance with the EU guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary use, Annex 13 [46], local regulations, and trial requirements. Label text will be translated into local languages as required.

9.8.2 Storage of trial products

Storage of IMP

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

The IMPs must be stored protected from light at 2 to 8°C and remain in the original container until used at the site. The temperature during storage must be monitored by a calibrated,

stationary, and continuously monitoring system. Minimum requirement is a calibrated min/max thermometer.

A temperature log must be kept documenting the storage within the right temperature interval. Storage facilities should be checked at least every working day. In case of temperature excursions upon receipt or during storage, please refer to the Trial Product Handling Manual supplied by LEO Pharma.

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

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

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

Damaged IMP should not be used.

9.8.3 Investigational medicinal product accountability

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

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

Documentation of IMP accountability must be kept for the IMPs administered to each individual subject randomised in the trial. This documentation must be available during monitoring visits and will be checked by an unblinded CRA to verify correct administration of the IMPs. Drug accountability information will be recorded by unblinded site staff for individual drug accountability per subjects as well as for the inventory status of all IMPs at the trial site on paper forms.

All [unused] IMPs (including packaging material) supplied by the contract manufacturing organisation (CMO) on behalf of LEO Pharma will be returned to the CMO. Prior to their return, the IMP must be fully accounted for by the unblinded CRA with the help of the unblinded site staff. Accountability must be documented on drug accountability forms.

IMPs will be returned from the trial site to the CMO directly. For more information about handling of IMPs at site, including drug accountability and reconciliation, please refer to the Trial Product Handling Manual.

9.8.4 Treatment compliance

IMP injections will be performed by unblinded site staff who will document the total number of injections administered per treatment day in the eCRF.
In case of non-compliance, details which injection was not administered in the comparator treatment group (i.e., Dupixent® or saline) will be documented as specified in the blinding plan.

Reporting in eCRF

The following data will be recorded in the eCRF:

- IMP application according to dosing schedule (yes, no); If no, a reason will be given.
- Primary reason for non-compliance – lack of time, adverse event, other (if other, a specification should be provided).
- Date and time of injections (stated for each of the injections per visit separately).
- Site of injection: For the site (upper leg [thigh], stomach area [abdomen] or in the upper, outer arm) the laterality should be specified (right or left).

9.8.5 Trial product destruction

All used LEO 138559 vials and unused IMP must be returned to the CMO and will be destroyed by the CMO according to approved procedures and/or local requirements.

Empty comparator syringes and syringes used for administration of IMP and saline solution can be destroyed at site provided the trial site has procedures in place for such destruction.

Trial sites which do not have such IMP destruction procedures in place will dispose used IMP syringes in sharps bins which will be shipped to the CMO.

9.9 Provision for subject care following trial completion

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

9.10 Reporting product complaints

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

Critical complaints (defined as any defect, issue, that has or potentially could have a serious impact on the subject [e.g. SAE or large particles in the vial) must be reported to the Quality department via Global Safety within 24 hours of knowledge.

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

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

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

Fax number: +45 6910 2468

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

10 Discontinuation and withdrawal

10.1 General principles

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

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

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

10.2 Reasons for discontinuation of IMP

10.2.1 Reasons for permanent discontinuation of IMP

Subjects will permanently discontinue IMP in the event of:

- Withdrawal by subject
- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.
- Confirmed clinically significantly abnormal ECG or change in ECG.
- Initiation of prohibited medication which cannot be safely replaced by other non-prohibited medications.
- Evidence of pregnancy, or if the subject is noncompliant with the contraception requirements (see Section 8.2).
- Symptomatic infection with SARS-CoV-2 that is likely to have an impact on efficacy or safety data (i.e., patients with a SARS-CoV-2 infection without or very mild symptoms only (e.g., rhinitis or sore throat) might continue with the study at investigator's discretion and in accordance with the applicable local regulations)..
- Other reasons, at the discretion of the investigator. If other, a specification should be provided.

It is not allowed to restart IMP treatment after discontinuation of IMP.

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 where the following options are available:

- Death.
- Pregnancy.
- Adverse event.
- Use of prohibited concomitant medication
- Lack of efficacy.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

If 'adverse event' or 'other' is selected, a specification must be provided in the eCRF. If adverse event is selected, the AE in question will be linked to the IMP discontinuation.

If 'withdrawal by subject' is selected, it will be recorded whether the subject withdrew informed consent or not.

Discontinuation of IMP due to COVID-19 pandemic will be collected and specified in the 'Other' category.

10.2.2 Reasons for temporary discontinuation of IMP

IMP dosing may be temporarily suspended in the event of:

- COVID-19 related disruption leading to site closure.

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

10.3 Early termination assessments

Permanent discontinuation of IMP

Subjects who permanently discontinue IMP for any reason will be asked to attend an early termination visit as soon as possible after last administration of IMP and return to the trial site for additional visits as indicated below:

- An early IMP termination visit as soon as possible after last dose of IMP (in case of early termination before week 4: a nominal week 4 visit)
- An end of trial visit (safety follow-up visit 16 weeks after last administration of IMP).

See the schedule of trial procedures (Section 4) for data to be collected at these visits. The subjects will be asked to complete the diary until end of trial visit. The investigator will review any AEs which will be followed up according to Section 13.7, if the subject agrees.

Details on data to be recorded in the eCRF for subjects who permanently discontinue IMP can be found in Section 11.8.

Withdrawal from trial

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

Details on data to be recorded in the eCRF for subjects who withdraw from the trial can be found in Section 11.8.

10.4 Lost to follow-up

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

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

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

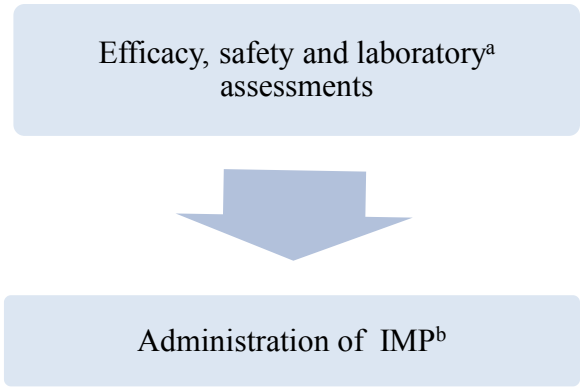
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

11 Trial assessments and procedures

11.1 Overview

Assessments and procedures to be conducted at each visit are listed in the schedule of trial procedures (Section 4) and will be conducted in the order presented in Panel 6.

Panel 6: Sequence of assessments



Abbreviations: IMP = investigational medicinal product.

a. Laboratory assessments include PK and PD samples. PD samples include serum biomarkers, skin biopsies and tape strips.
b. For the first 3 treatment visits (i.e., Visits 3, 4, and 5) subjects will be monitored after injections for immediate drug reactions for a minimum of 1 hour with vital signs taken immediately after injections as well as after 30 minutes (± 5 minutes) and after 1 hour (± 5 minutes), or until stable, whichever is later.

Subjects participating in the trial will be under careful supervision of a qualified principal investigator who must be a dermatologist or an allergist. Investigators must be physicians and have experience in treating AD as well as documented experience with and/or training in the assessments used in this trial. All dermatologic assessments must be performed by a dermatologist or an adequately qualified medical doctor (defined as someone with at least 1 year post graduate experience).

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

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

The investigators performing the assessments must not be involved in the preparation and administration of IMP (Section 9.3.2).

11.2 Assessments performed only at screening/baseline

11.2.1 Demographics

The following demographic data will be recorded:

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

11.2.2 Medical history

Relevant medical history must be recorded:

- Skin disease history and atopy history including:
  - Age at first onset of AD.
  - Asthma.
  - Food allergy.
  - Hay fever.

  For each condition or diagnosis, the start date and stop date will be recorded (it will also be recorded if the diagnosis is ongoing).
- Other medical and surgical history including concurrent diagnoses within the previous 12 months. For each condition, diagnosis, or surgical procedure, the start date and stop date will be recorded (it will also be recorded if the condition, diagnosis, or surgical procedure is ongoing).

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

11.2.3 Height

The subject’s height (without shoes) will be measured according to the schedule of trial procedure (Section 4).

11.3 Efficacy assessments

11.3.1 Validated Investigator Global Assessment Scale for Atopic Dermatitis

The validated Investigator Global Assessment Scale for Atopic Dermatitis (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 7) [47]. The vIGA-AD score will be assessed according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. The disease severity assessment score will be recorded in the eCRF.

Panel 7: Validated Investigator Global Assessment Scale for Atopic Dermatitis

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

11.3.2 Body surface area involvement

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

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

11.3.3 Eczema Area and Severity Index

The Eczema Area and Severity Index (EASI) is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD [48]. The EASI score will be assessed according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit.

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

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

Panel 8: Calculation of the EASI score

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

Abbreviations: AS = area score; EASI = Eczema Area and Severity Index; SS = severity score.
Modified from [49].

Panel 9: EASI severity score scale and area score scale

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

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

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

Abbreviations: EASI = Eczema Area and Severity Index.

11.4 Safety assessments

11.4.1 Vital signs

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

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

Vital signs (blood pressure, pulse, and body temperature) will be assessed following at least 5 minutes of rest. If a subject presents with an abnormal vital sign, the measurement of the vital sign can be repeated approximately 2–5 minutes later to verify the first measurement. Should the repeated measurement result in a normal value, the measurement must be repeated once more. If the third measurement verifies the second (normal) value, the first measurement should be considered false and the third measurement should be recorded in the eCRF. If the third measurement confirms the first measurement (abnormal), the second measurement should be considered false and the third measurement should be recorded in the eCRF. Only the last measurement considered true should be recorded in the eCRF.

In case of a clinically significant abnormal vital sign at screening and/or baseline, it will be at the discretion of the investigator if the subject should be included in the trial in accordance

with exclusion criterion 31. 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; if not, a reason should be provided. Vital signs, arm used to measure blood pressure, the temperature measuring method (axillary, ear, oral, rectal, other), and the date and time vital signs were measured will be recorded in the eCRF. Clinically significant abnormal vital signs at the screening visit and baseline (as the subjects has not been administered treatment) will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom, or illness occurring after randomisation will be reported as an AE in accordance with Section 13.3.

11.4.2 Physical examination

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

In case of a clinically significant abnormal finding during physical examination at screening and/or baseline, it will be at the discretion of the investigator if the subject should be included in the trial in accordance with exclusion criterion no. 31. During the trial, if a subject presents with a clinically significant abnormal finding during physical examination, the investigator must take appropriate action, at their discretion.

Reporting in eCRF

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

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

11.4.3 Weight

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

11.4.4 Electrocardiography

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

At the respective visit, the individual measurements as well as the average of 3 consecutive 12-lead resting digital ECG will be recorded after the subject has been in supine position for at least 5 minutes. ECGs must be measured before any blood samples scheduled at the same visit.

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

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

The investigator must evaluate all abnormal ECG results ('clinically significant' or 'not clinically significant') and sign and date. The investigator is responsible for taking the final decision about the clinical significance of any abnormal ECG.

If a result is abnormal at the screening or baseline visit and considered by the investigator to be clinically significant, it will be up to the investigator's discretion to decide if the subject should be enrolled into the trial (respecting exclusion criteria no. 21 and 31). If a subject with an abnormal and clinically significant ECG result is enrolled, the investigator should provide a justification in the medical record.

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

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

Reporting in eCRF

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

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

11.4.5 Laboratory testing

11.4.5.1 Overview

Pregnancy tests in female subjects of child-bearing potential must be performed at visits according to the schedule of trial procedures (Section 4). At visit 1 (screening), a serum hCG test is to be made, on the other visits, urine hCG dip tests will be made. At visit 3 (baseline), the test must be made prior to randomisation. Pregnant women must not be randomised into the trial.

Blood and urine samples will be collected according to the schedule of trial procedures (Section 4) and the evaluations listed in Panel 10 will be performed.

Panel 10: Clinical laboratory tests

Clinical chemistry	Haematology[2]
Sodium	Haematocrit
Potassium	Haemoglobin
Creatinine	Leukocytes
Urea nitrogen	Neutrophils
Calcium	Neutrophils/leukocytes[5]
Alkaline phosphatase	Lymphocytes
Aspartate aminotransferase (AST)	Lymphocytes/leukocytes[5]
Alanine aminotransferase (ALT)	Monocytes
Gamma glutamyl transferase	Monocytes/leukocytes[5]
Bilirubin[1]	Eosinophils
(Direct bilirubin)[1]	Eosinophils/leukocytes[5]
(Indirect bilirubin)[1]	Basophils
Cholesterol	Basophils/leukocytes[5]
LDL cholesterol	Thrombocytes

HDL cholesterol Triglycerides Glucose (non-fasting) Albumin Protein Tryptase[2] Lactate dehydrogenase C-reactive protein Amylase	**Serology[3]** Hepatitis B virus surface antigen Hepatitis B virus surface antibody Hepatitis B virus core antibody Hepatitis C virus antibody HIV-1 antibody HIV-2 antibody **Tuberculosis test[3, 7]** *Mycobacterium tuberculosis* IFN-γ release assay
Urinalysis[4] Protein Glucose Ketones Occult blood Leukocytes Nitrite	**Serum pregnancy test[3,6]** Choriogonadotropin beta **Urine pregnancy test[6, 7]** Choriogonadotropin beta dip stick

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

Abbreviations: HDL = high density lipoprotein; HIV = human immunodeficiency virus; IMP = investigational medicine product; LDL = low density lipoprotein; SC = subcutaneous.

11.4.5.2 Investigator evaluation of laboratory samples

Central laboratory

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

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

If a screening laboratory result is abnormal and of clinical significance, it will be at the investigator's discretion to decide if the subject should be randomised into the trial. During the trial, if a subject presents with a clinically significant abnormal laboratory result, appropriate action, as judged by the investigator, must be taken.

Serum pregnancy tests for women of childbearing potential will be analysed by a central laboratory, which will provide results to the trial sites. A positive serum pregnancy test at screening is an exclusion criterion.

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

Tests performed at the trial site

Subjects will have a test on tuberculosis (*Mycobacterium tuberculosis* IFN-γ release assay) at screening (Visit 1). A positive or indeterminate test result is an exclusion criterion.

Urine samples will be tested with a dipstick according to the schedule of trial procedures (Section 4). 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.

Women of childbearing potential will have a urine pregnancy test performed at the trial site at baseline prior to randomisation. The test will be repeated as shown in the schedule of trial procedures in Section 4. A positive urine pregnancy test must be verified with a serum pregnancy test. A woman with a positive urine pregnancy test during the trial must immediately discontinue IMP and must be withdrawn from the trial after confirmation by positive serum pregnancy test.

Reporting in eCRF

At each visit, the site staff will record 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 be recorded in the eCRF.

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 performed. If not, a reason should be provided. Also, the date and the outcome of the urine pregnancy test will be recorded in the eCRF ('positive', 'negative').

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

11.4.6 Anti-drug antibodies measurements

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

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

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

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

Reporting in eCRF
It will be recorded in the eCRF if an ADA blood sample was taken. If not, a reason should be provided.

11.5 Pharmacokinetic assessments

11.5.1 Blood sampling for analysis of PK

Blood samples for PK assessments will be collected at the time points specified in the schedule of trial procedures (Section 4). PK blood sampling should be performed prior to IMP administration at site. Date and time of sample collection will be captured on the laboratory requisition forms.

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

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

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

11.6 Pharmacodynamics assessments

11.6.1 Overview

Biomarker expression in blood and skin (skin biopsies and tape strips) will be measured to evaluate treatment effect of LEO 138559 on disease biomarkers and investigate gene expression in the skin related to the mechanism of action of LEO 138559 and Dupixent®.

Blood and skin samples for PD assessment must be collected at the time points specified in the schedule of trial procedures (Section 4).

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

11.6.2 Blood biomarkers

Evaluation of effects of treatment of AD patients with LEO 138559 or Dupixent® on protein biomarkers in blood, including but not limited to E- selectin, PI3/Elafin, CCL7, IL-16, and newly identified IL-22BP [50] will be performed on serum samples. Changes in blood biomarkers have been linked to atopic dermatitis in previous disease signature studies [51]. Serum samples for biomarker analyses will be taken according to the schedule of trial procedures (Section 4).

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

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

Reporting in eCRF

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

11.6.3 Skin biopsies

Lesional skin biopsies from subjects treated with LEO 138559 or Dupixent® will be evaluated by single-cell RNASeq analysis, a technique which enables evaluation of global gene expression in single cells and which has previously been used in a study in subjects with AD treated with Dupixent® [52]. Effects of LEO 138559 on single-cell transcriptomics have not been evaluated to date. Histological analysis will also be performed, on the same biopsies.

One 5 mm skin punch biopsy will be taken at each time-point specified in the schedule of trial procedures (Section 4) for analysis of differentially expressed genes analysed by single cell RNA sequencing and for AD biomarker analysis.

At baseline, the biopsy will be taken from a representative lesional area. At the end-of-treatment visit (or early IMP termination visit, if applicable) the same lesional area as at baseline ("original lesional area") will be sampled. Note that the lesion sample at the end-of-treatment (or early IMP termination visit, if applicable) should be taken from the original lesional area, even if this lesion clears during the trial. At the other sampling timepoint a biopsy may be taken from any other representative lesion.

Photographs will be taken of the biopsy sites prior to each biopsy sampling.

A check of skin biopsy wound healing including removal of suture, if applicable, will be performed at the next trial visit. After the biopsy at week 16 visit, subjects will be asked to return to site for suture removal two weeks later (week 18) or alternatively to have the sutures removed by their general practitioner, as preferred by subject.

Collection, handling, and shipment instructions for skin biopsy samples for single cell RNA sequencing and evaluation of biomarkers are provided in a separate laboratory manual.

Skin biopsy single cell RNA sequencing and biomarker data will be described in detail in a separate report appended to the CTR

Reporting in eCRF
For each skin biopsy it will be recorded in the eCRF from which body location (upper limb, lower limb, trunk) it was taken. If a skin biopsy was not taken, a reason will be provided.

11.6.4 Skin tape strips

The effects of treatment of AD patients with LEO 138559 and Dupixent® on biomarkers that have been linked to the integrity of the skin barrier will be evaluated by analysis of non-invasive tape strips from lesional skin, a technique that has been used to demonstrate a link between decreased levels of ceramides in the stratum corneum and barrier- disrupted dry skin in AD patients [53].

Tape stripping will be performed according to the schedule of trial procedures (Section 4).

Non-invasive tape stripping will be done for biomarker analyses in the skin. At baseline, the samples will be taken from a representative lesional area. At the end-of-treatment visit (or early IMP termination visit, if applicable) the same lesional area as at baseline ("original

lesional area") will be sampled. Note that the lesion sample at the end-of-treatment (or early IMP termination visit, if applicable) should be taken from the original lesional area, even if this lesion clears during the trial. At the other sampling timepoint tape stripping will be performed from any other representative lesion.

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

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

Reporting in eCRF

For each tape strip visit it will be recorded in the eCRF from which body location (upper limb, lower limb, trunk) the tape strips were collected. If a tape stripping was not performed, a reason will be provided

11.7 Other assessments

11.7.1 Patient-reported outcomes

11.7.1.1 Diary

The subjects will receive a paper diary at screening (visit 1) and must complete the diary each day throughout the trial starting at least 7 days before baseline (visit 3, day 0). Subjects should document the use of emollients as well as use of other medications (except usual ongoing medication). Compliance with the diary completion will be reviewed by the trial site staff at the site visits and completed diary pages will be collected and the corresponding information from the diary will be entered into the eCRF by trial site staff. The diary should be returned to the trial site as outlined in the schedule of trial procedures (Section 4).

11.7.1.2 Worst Daily Pruritus numeric rating scale

Subjects will assess their worst itch severity over the past 24 hours using an 11-point NRS ('Worst Daily Pruritus NRS') with 0 indicating 'no itch' and 10 indicating 'worst itch imaginable'. Subjects will complete the Worst Daily Pruritus NRS as part of a paper diary each day in the morning starting at least 7 days prior to baseline (visit 3) until week 32 (visit 16).

11.8 End of trial

End-of-treatment form

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

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

End-of-trial form

An end-of-trial form must be completed in the eCRF for all screened subjects. The following data will be collected:

- Screening failure.
- Did the subject complete the trial?
- Which was the last visit (including phone calls) the subject attended in this trial?
- Date of last contact.
- Primary reason for withdrawing from the trial (death, pregnancy, adverse event, lack of efficacy, screening failure, withdrawal by subject, lost to follow-up, or other [if other, a specification should be provided]).
- If the subject attended the primary endpoint visit (visit 6). If not, the primary reason for not attending the visit (death, pregnancy, adverse event, lack of efficacy, withdrawal by subject, lost to follow-up, or other [if other, a specification should be provided]).
- If the subject attended the end-of-treatment visit (visit 12). If not, the primary reason for not attending the visit (death, pregnancy, adverse event, lack of efficacy, withdrawal by subject, lost to follow-up, or other [if other, a specification should be provided]).
- If the subject attended the safety follow-up visit (visit 16). If not, the primary reason for not attending the visit (death, pregnancy, adverse event, lack of efficacy, withdrawal by subject, lost to follow-up, or other [if other, a specification should be provided]).

The end of trial form will be completed when the subject turned out to be a screening failure or has had their last visit (that is the safety follow-up visit 16, or early IMP termination visit).

11.9 Estimate of total blood volume collected

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

11.10 Storage of biological samples

Laboratory samples (chemistry/haematology/serology) will not be stored for more than a few days after sampling and analysis.

Primary samples for PK will be discarded by the bioanalytical lab upon finalisation of the CTR whereas backup samples stored at the Central Lab will be retained for as long as the quality of the material permits evaluation but for no longer than 6 months after completion of the CTR. Any backup samples that have been sent to the Bioanalytical Lab will also be discarded upon finalisation of the CTR.

Primary samples (set A samples) for ADA evaluation will be discarded by the bioanalytical lab upon finalisation of the CTR whereas backup samples (set B samples) stored at the central laboratory will be stored at least until approval in first major market (US or EU or JP) or until 10 years after final CTR– which ever comes last.

Biomarker samples (skin biopsies, skin tape strips and PD blood samples) will be retained for as long as the quality of the material permits evaluation but for no longer than 12 months after completion of the CTR.

12 Scientific rationale for trial design and appropriateness of assessments

12.1 Scientific rationale for trial design

LP0145-2274 is a randomized, double-blinded, active comparator-controlled, 16-week, single-site exploratory, mechanistic trial designed to evaluate the effect on the molecular signature of SC administered LEO 138559 450 mg Q2W compared with Dupixent® Q2W in adults with moderate to severe AD.

The primary endpoint is selected to gain information about the mode of action of LEO 138559 and the influence of blocking of IL-22 pathway on gene expression in lesional skin.

Based on PK, PD, and safety results of the FiM trial with LEO 138559 (LP0145-1315), the dose regimen LEO 138559 450 mg Q2W was selected for investigation in this trial. In addition to the Q2W dosing schedule, an additional dose of IMP will be given to the subjects at week 1 to reach steady state exposure early in the treatment period. According to a PK model developed based on preliminary data from the FiM trial, the additional dose given at week 1 should allow 75% of steady state exposure to be reached already after 3 weeks of treatment. The 16-week treatment period was selected to ensure sufficient time to evaluate the impact of LEO 138559 on disease severity as AD. Further, given the expected half-life, dosage, and dosing frequency of LEO 138559, it is expected that LEO 138559 achieve steady state concentration before the end of this period and a maximum therapeutic effect will be achieved by this time. A safety follow-up period of 16-week after last dose of IMP is considered an appropriate length as serum concentrations of LEO 138559 are expected to be declined to nondetectable levels (below the lower limit of quantification) in most subjects at that timepoint.

The use of Dupixent® as a comparator will serve as reference to evaluate the mode of action, efficacy and safety of LEO 138559. The comparison with an approved immunoregulatory agent that selectively and simultaneously inhibits IL-4 and IL-13 allows for an evaluation of similarity or differences in the mechanistic effect. Dupixent® will be administered according to the prescription instructions (standard of care) for adult subjects with moderate to severe AD with an initial dose of 600 mg followed by Q2W injections with 300 mg.

Since both IMPs are distinguishable in appearance and dosing requirements (number of injections) this study will be performed as an assessor- and patient blinded trial. Only the person responsible for handling and administration of IMPs will be unblinded. The investigator responsible for assessment of safety and efficacy and the patient will be blinded throughout the study, to ensure that the clinical assessments will be carried out without bias. Therefore, certain blinding procedures are in place (see section 9.3.2)

The trial population is adult subjects with moderate to severe AD with documented inadequate response to topical AD treatments or being a subject for whom topical treatment is medically inadvisable. This trial population represents the subjects with highest remaining unmet clinical need and can be applied to the general population. The other eligibility criteria have been chosen to ensure inclusion of the targeted patient population and safety of the subjects and to minimize factors which could interfere with the efficacy and safety assessments.

12.2 Appropriateness of assessments

In order to gain more information about the mechanism of action of LEO138559, analysis of biomarkers in skin and blood will be performed to evaluate effects of treatment of subjects with atopic dermatitis with LEO 138559 or a comparator (Dupixent®). Lesional skin biopsies will be analyzed using single-cell RNASeq and histology while serum samples will be assessed for protein biomarkers.

Serum concentration of LEO 138559 will be measured to further characterise the PK of LEO 138559 in subjects with moderate to severe AD.

Efficacy will be evaluated by investigators assessment of EASI and vIGA-AD which are validated measures used in clinical practice and clinical trials [47-49].

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

13 Adverse events

13.1 Definition and classification of adverse events

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

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

13.2 Collection of adverse event reports

AE data must be collected from time of first trial-related activity after the subject has signed the informed consent form (ICF) until subject's completion of the clinical trial (safety follow-up visit at week 32 see Section 7.3)

AEs must be assessed by a physician.

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

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

13.3 Reporting of adverse events

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

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

The *duration* of the AE must be reported by the start date and stop date of the event, unless the event is ongoing. If the event is ongoing, it will be marked as ongoing. In addition, it will be recorded if the AE started prior to first administration of IMP.

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

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

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

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

Withdrawn from trial due to this AE: it must be recorded whether the AE led to withdrawal from the trial.

13.4 Reporting of serious adverse events

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

13.4.1 Investigator reporting responsibilities

Any SAE must be reported to LEO Pharma on the (paper) SAE form 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, comparator 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 anonymised reports of diagnostic procedures, hospital records, autopsy reports, etc.

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

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

SAEs occurring after the completion of the clinical trial, including any protocol-required post-treatment follow-up period, should not be routinely sought or recorded. However, such events should be reported immediately without undue delay and no later than 24 hours of obtaining knowledge to Global Safety at LEO Pharma (see contact details above) if the investigator becomes aware of them.

13.4.2 LEO Pharma reporting responsibilities

Global Safety at LEO Pharma is responsible for assessing whether an SAE is expected. The relevant reference safety information documents for this clinical trial are:

- For the drug product LEO 138559, the investigator's brochure Section 7.3.8, edition 4 and subsequent updates must be used.
- For the comparator Dupixent® the latest version of the SmPC [54] must be used.

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

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

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

13.5 Other events that require expedited reporting

13.5.1 Pregnancy

Any pregnancy, occurring after first exposure to IMP and until the subject has completed the trial must be reported to LEO Pharma within 24 hours of first knowledge using the (paper)

pregnancy form (part I). All pregnancies must be followed up until delivery or termination, and outcome must be reported on the (paper) pregnancy form (part II) within 24 hours of first knowledge.

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

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

13.6 Reporting of other events

13.6.1 Medication error

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

Medication errors include accidental overdose or underdose, inappropriate schedule of product administration, incorrect route of product administration, wrong product administered, and expired product administered.

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

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

Reporting in eCRF

Medication error must be recorded on the AE from 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 (Section 13.4).

13.6.2 Misuse or abuse

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

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

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

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

13.6.3 Aggravation of condition

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

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

13.7 Follow-up for final outcome of adverse events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). Once a subject leaves the clinical trial, the investigator should follow up on the outcome of all non-serious AEs classified as possibly or probably related to the IMP for 2 weeks after visit 16 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 stabilised and from which the subject cannot be expected to recover during the trial or the safety follow-up periods, e.g. chronic or stabilised conditions, the final outcome at the investigator's discretion should be reported as 'recovering/resolving' or 'not recovered/not resolved'. In addition, a statement detailing why the subject cannot be expected to recover during the trial, e.g. that the SAE has stabilised or is chronic, should be added to the narrative description of the SAE on the SAE form.

13.8 Handling of an urgent safety measure

An urgent safety measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined as *"…the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event*

is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard." [56].

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

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

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

14 Statistical methods

14.1 Sample size

The sample size of 12 subjects evaluable for the primary endpoint i.e., for whom a lesional biopsy is available at baseline and week 4 (8 receiving LEO 138559 and 4 receiving comparator) is based on the trial design for the exploratory comparison of the molecular signature changes of LEO 138559 and the comparator. The sample size is not based on power calculations.

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

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

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

A PK analysis set will be defined as all subjects who were exposed to LEO 138559 and provided at least one sample for measuring serum concentrations of LEO 138559.

The decisions regarding inclusion/exclusion of subjects or subject data from the trial analysis sets will be documented in the clinical trial report.

14.3 Statistical analysis

14.3.1 Disposition of subjects

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

A subject disposition summary table will be made including information of number of subjects who were screened, randomised, exposed and who completed the trial, permanently discontinued IMP, and/or were withdrawn from the trial (by treatment group and overall)

14.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects and by treatment group and overall. Presentations of age, sex,

ethnicity, race, and baseline EASI score by treatment group will be reported for all randomised subjects. Other baseline characteristics include height, weight, BMI, duration of AD, concurrent diagnoses (from medical history and indications for concomitant medication), concomitant medication, and previous AD treatments.

14.3.3 Exposure and treatment compliance

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

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

Treatment compliance will be presented for the safety analysis set per treatment group as the percentages of missed IMP doses. In addition, the percentage of subjects who received IMP application according to dosing schedule will be presented per treatment group.

14.3.4 Testing strategy

No formal statistical significance tests will be carried out.

14.3.5 Primary endpoint analysis

The primary endpoint

- Change in biomarkers in lesional skin biopsies typically associated with atopic dermatitis from baseline to week 4

will be analyzed descriptively by computing the following statistics by treatment group: minimum and maximum value, lower and upper quartile, median, mean, standard deviation and median absolute deviation.

Individual and mean data as well as boxplots will be plotted by treatment group.

14.3.6 Secondary endpoint analysis

The secondary endpoint

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

will be analysed descriptively on the safety analysis set by computing the number of treatment-emergent adverse events per subject by treatment group.

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.

14.3.7 Analysis of exploratory efficacy endpoints

Binary endpoints

The endpoints

- Having a decrease in EASI of at least 50% (EASI 50) from baseline to week 1, 2, 4, 6, 8, 12, and 16, assessed separately.
- Having a decrease in EASI of at least 75% (EASI 75) from baseline to week 1, 2, 4, 6, 8, 12, and 16, assessed separately.
- Having a decrease in EASI of at least 90% (EASI 90) from baseline to week 1, 2, 4, 6, 8, 12, and 16, assessed separately.
- Having vIGA-AD score of 0 (clear) or 1 (almost clear) at week 1, 2, 4, 6, 8, 12, and 16, assessed separately.

will be analysed on the full analysis set by computing frequency tables for each time point by treatment group.
Proportions with respect to these endpoints will be plotted by treatment group.

Continuous endpoints

The endpoints

- Change in EASI score from baseline to week 1, 2, 4, 6, 8, 12, and 16.
- Change in Worst Daily Pruritus NRS (weekly average) from baseline to weeks 1, 2, 4, 6, 8, 12, and 16.

will be analysed on the full analysis set by computing descriptive summary statistics for each time point by treatment group.

Individual and mean data as well as boxplots with respect to these endpoints will be plotted by treatment group.

14.3.8 Pharmacodynamics analysis

For the following endpoints;

- Change in expression of AD disease biomarkers in serum from baseline to week 1, 4, and 16.
- Change in expression of AD disease biomarkers in skin biopsies from baseline to week 1, 4, and 16.
- Change in expression of AD disease biomarkers in skin tape strips from baseline to week 1, 4, and 16.

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

14.3.9 Safety analysis

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

14.3.9.1 Adverse events

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

Treatment-emergent AEs will be summarised; however, all AEs recorded during the course of the trial will be included in subject data listings. The tabulations described in the following will only include the treatment-emergent AEs. In each of the tabulations, AEs are defined by MedDRA preferred terms within primary SOC.

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

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

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

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

The number of AEs and number of subjects with each type of AEs will be tabulated by treatment group from baseline to week 16, from baseline to week 32, and from week 17 to week 32.

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

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

14.3.9.2 Vital signs and physical examination

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

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

14.3.9.3 ECG

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

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

14.3.9.4 Clinical laboratory evaluation

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

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

14.3.9.5 Anti-drug antibodies

For the exploratory endpoint

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

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

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

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

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

14.3.10 Pharmacokinetic analysis

The endpoint

- Serum concentration of LEO 138559 at weeks 0, 1, 4, 8, 12, 16, and 32, assessed separately.

will be evaluated based on the PK analysis set.

LEO 138559 serum concentrations will be listed and summarized by visit. The serum concentrations will be included in a cross-trial population PK analysis and reported separately.

14.3.11 Interim analysis

No interim analysis is planned.

14.3.12 General principles

All data will be analysed descriptively. No formal significance tests will be performed. Efficacy analyses will be based on the FAS, and safety analyses will be based on the safety analysis set. PK summary will be based on the PK analysis set.

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

An observed cases approach will be used for tabulations of data by visit (that is, involving only those subjects who attended each specific visit). The number of subjects for whom data was not collected at each specific visit will also be provided.

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

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

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

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

14.3.13 Handling of missing values

Handling of missing values will be specified in the statistical analysis plan (SAP).

For the weekly average of worst daily pruritus NRS, a minimum of four measurements per week must be available, otherwise the score for this week will be set to missing.

15 References

1. Weidinger, S., et al., *Atopic dermatitis.* Nat Rev Dis Primers, 2018. **4**(1): p. 1-20.
2. *LEO Pharma A/S. Investigator's Brochure - LEO 39652 (Atopic Dermatitis)*. 0.2 nd ed. 2014.
3. Dalgard, F.J., et al., *The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries.* J Invest Dermatol, 2015. **135**(4): p. 984-991.
4. Kiebert, G., et al., *Atopic dermatitis is associated with a decrement in health-related quality of life.* Int J Dermatol, 2002. **41**(3): p. 151-8.
5. Deckers, I.A., et al., *Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies.* PLoS One, 2012. **7**(7): p. e39803.
6. Abuabara, K., et al., *The prevalence of atopic dermatitis beyond childhood: A systematic review and meta-analysis of longitudinal studies.* Allergy, 2018. **73**(3): p. 696-704.
7. Silverberg, J.I. and J.M. Hanifin, *Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study.* J Allergy Clin Immunol, 2013. **132**(5): p. 1132-8.
8. Salimi, M., et al., *A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis.* J Exp Med, 2013. **210**(13): p. 2939-50.
9. Soumelis, V., et al., *Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP.* Nat Immunol, 2002. **3**(7): p. 673-80.
10. Mashiko, S., et al., *Increased frequencies of basophils, type 2 innate lymphoid cells and Th2 cells in skin of patients with atopic dermatitis but not psoriasis.* Journal of Dermatological Science, 2017. **88**(2): p. 167-174.
11. Brüggen, M.C., et al., *In Situ Mapping of Innate Lymphoid Cells in Human Skin: Evidence for Remarkable Differences between Normal and Inflamed Skin.* J Invest Dermatol, 2016. **136**(12): p. 2396-2405.
12. Maggi, L., et al., *Human circulating group 2 innate lymphoid cells can express CD154 and promote IgE production.* J Allergy Clin Immunol, 2017. **139**(3): p. 964-976.e4.
13. Gittler, J.K., et al., *Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis.* J Allergy Clin Immunol, 2012. **130**(6): p. 1344-54.
14. Nograles, K.E., et al., *IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells.* J Allergy Clin Immunol, 2009. **123**(6): p. 1244-52 e2.
15. Suarez-Farinas, M., et al., *Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis.* J Allergy Clin Immunol, 2013. **132**(2): p. 361-70.
16. Eichenfield, L.F., et al., *Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies.* J Am Acad Dermatol, 2014. **71**(1): p. 116-32.

17. Kim, B.S., et al., *Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream.* Journal of Allergy and Clinical Immunology, 2020. **145**(2): p. 572-582.
18. Nakagawa, H., et al., *Delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with moderate to severe atopic dermatitis: A phase 3, randomized, double-blind, vehicle-controlled study and an open-label, long-term extension study.* J Am Acad Dermatol, 2020. **82**(4): p. 823-831.
19. Japan Tobacco Inc, *Japan Tobacco delgocitinib (Corectim®) PMDA approval (30200AMX00046000)*. 2020.
20. Sidbury, R., et al., *Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents.* J Am Acad Dermatol, 2014. **71**(2): p. 327-49.
21. Haeck, I.M., et al., *Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial.* J Am Acad Dermatol, 2011. **64**(6): p. 1074-84.
22. Schram, M.E., et al., *A randomized trial of methotrexate versus azathioprine for severe atopic eczema.* J Allergy Clin Immunol, 2011. **128**(2): p. 353-9.
23. Davari, D.R., et al. *Current Perspectives on the Systemic Management of Atopic Dermatitis*. Journal of asthma and allergy, 2021. **14**, 595-607 DOI: 10.2147/jaa.s287638.
24. Guttman-Yassky, E., *Lebrikizumab, a High-Affinity IL-13 Inhibitor, Improves Clinical Manifestations in Moderate-to-Severe Atopic Dermatitis: Primary Results From a Randomized, Double-Blinded, Placebo-Controlled, Dose-Ranging, Phase 2b Study.* 2019.
25. Kabashima, K., et al., *Nemolizumab in patients with moderate-to-severe atopic dermatitis: Randomized, phase II, long-term extension study.* J Allergy Clin Immunol, 2018. **142**(4): p. 1121-1130.e7.
26. Wollenberg, A., et al., *Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb.* J Allergy Clin Immunol, 2019. **143**(1): p. 135-141.
27. Silverberg, J.I., et al., *Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial.* JAMA Dermatology, 2020. **156**(8): p. 863-873.
28. Guttman-Yassky, E., et al., *Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study.* J Am Acad Dermatol, 2018. **S0190-9622**(18): p. 30129-4.
29. Guttman-Yassky, E., et al., *Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial.* J Allergy Clin Immunol, 2020. **145**(3): p. 877-884.
30. European Medicines Agency, *Baricitinib; assessment report (EMA/13493/2017 and EMEA/H/C/004085/0000)*. 2016.
31. Simpson, E.L., et al., *Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials.* Br J Dermatol, 2020. **183**(2): p. 242-255.
32. Thijs, J.L., et al., *Moving toward endotypes in atopic dermatitis: Identification of patient clusters based on serum biomarker analysis.* J Allergy Clin Immunol, 2017. **140**(3): p. 730-737.

33. Bieber, T., et al., *Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go?* J Allergy Clin Immunol, 2017. **139**(4s): p. S58-s64.
34. Wolk, K., et al., *Biology of interleukin-22.* Semin Immunopathol, 2010. **32**(1): p. 17-31.
35. Kotenko, S.V., et al., *Identification, cloning, and characterization of a novel soluble receptor that binds IL-22 and neutralizes its activity.* J Immunol, 2001. **166**(12): p. 7096-103.
36. LEO Pharma A/S, *Investigator's Brochure, LEO 138559 in Atopic Dermatitis, project LP0145 (edition 4.0)*. 2021.
37. WMA, *World Medical Association. Declaration of Helsinki – ethical principles for medical research involving human subjects. Amended by the 64th WMA General Assembly, Fortaleza, Brazil*. 2013.
38. ICH, *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice. (E6)(R2), Step 4; 09-Nov*. 2016.
39. Argenx, B.V., *Summary of all the in vitro and in silico characteristics of ARGX112 (230C9_N297Q).*
40. *FDA: Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency.* March 2020; Updated on August 30, 2021.
41. *EMA: Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials.* 25-MAR-2020. **DRAFT**.
42. *FAQ - COVID-19 Studien - BASG (https://www.basg.gv.at/gesundheitsberufe/klinische-studien/klinische-studien-und-covid-19/haeufige-fragen)*
43. Schulz, K.F., D.G. Altman, and D. Moher, *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* Bmj, 2010. **340**: p. c332.
44. Johansson, S.G., et al., *Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003.* J Allergy Clin Immunol, 2004. **113**(5): p. 832-6.
45. Sampson, H.A., et al., *Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium.* J Allergy Clin Immunol, 2006. **117**(2): p. 391-7.
46. *European Commission. EudraLex: The Rules Governing Medicinal Products in the European Union. Guidelines for good manufacturing practices for medicinal products for human and veterinary use. Volume 4. 2010*
47. Eli Lilly and Company, *Validated Investigator Global Assessment scale for Atopic Dermatitis. vIGA-AD™.* 2017.
48. Hanifin, J.M., et al., *The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group.* Exp Dermatol, 2001. **10**(1): p. 11-8.
49. HOME, *Harmonising Outcome Measures for Eczema. Eczema Area and Severity Index (EASI) case report form. Aged 8 and over.* 2017.
50. Varandas, C., et al., *Serum IL-22 binding protein as a marker for atopic dermatitis activity and response to dupilumab treatment.* Clinical & Experimental Allergy, 2022. **52**(6): p. 820-823.

51. Brunner, P.M., et al., *The atopic dermatitis blood signature is characterized by increases in inflammatory and cardiovascular risk proteins.* Sci Rep, 2017. **7**(1): p. 8707.
52. Bangert, C., et al., *Persistence of mature dendritic cells, T_H2A, and Tc2 cells characterize clinically resolved atopic dermatitis under IL-4Rα blockade.* Science Immunology, 2021. **6**(55): p. eabe2749.
53. Imokawa, G., et al., *Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin?* J Invest Dermatol, 1991. **96**(4): p. 523-6.
54. Dupixent®, *Summary of Product Characteristics (SmPC), Nov-2021.*
55. ICH, *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Integrated addendum to ICH E6(R1): Guideline for good clinical practice E6(R2)*. 2016.
56. European Parliament Union and C.o.T. European, *Directive 2001/20/EC of the European Parlament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, 2001*, Ema, Editor. 2001.
57. ICH, *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Clinical Safety Data Management. Definitions and Standards for Expected Reporting (E2A), Step 4; 27-Oct.* 1994.
58. CIOMS, *International Ethical Guidelines for Health-related Research Involving Humans. Council for International Organizations of Medical Sciences*. 2016: Geneva.

Appendix 1: Definitions of adverse events and serious adverse events

Adverse event definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product [57].

This definition includes:

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

Serious adverse event definition

An SAE is any untoward medical occurrence that:

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

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

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

*Hospitalisation 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.

*Hospitalisation 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 hospitalisation are (S)AEs. If a complication prolongs hospitalisation, the event is an SAE.

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

Appendix 2: Classification of adverse events

Severity

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

Causality

The *causal relation* of the AE to the use of the IMP should be described in terms of probably, possibly, or not related according to the investigator's clinical judgement.

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

Outcome

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

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.

Appendix 3: Trial governance considerations

Appendix 3A: Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki [37] and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines [58].
- Current version of applicable International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines [55].
- EU General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

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

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

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

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

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

Appendix 3B: Informed consent process

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

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

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

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

Subject card

At randomisation, subjects will be provided with a card stating that they are participating in a clinical trial and which contains contact address and telephone numbers 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.

Appendix 3C: Subject and data confidentiality

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

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

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

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

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

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

Processing of personal data

This protocol specifies the personal data on trial subjects (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. In certain cases, an agreement on transfer of personal data may also be required.

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

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

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

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

Source data at trial sites

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

Source data should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data not normally collected as a routine part of the clinical practice at the site may be entered on a worksheet. 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.
- Randomisation code number.
- The fact that the subject is participating in a clinical trial in AD including treatment with LEO 138559 or Dupixent® for 16 weeks.
- Other relevant medical information.

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

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

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

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

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

site relevant to the clinical trial. This includes permission to examine, verify, and reproduce any records and reports that are important to the evaluation of the trial.

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

Data handling
Data will be collected by means of electronic data capture unless transmitted electronically to LEO Pharma or designee (e.g. laboratory data). The investigator or staff authorised by the investigator will enter subject data into an electronic CRF (eCRF). Data recorded in the eCRF will be accessible to the trial site and LEO Pharma personnel immediately after entry. The eCRF must be maintained in an up-to-date state by the trial site at all times.
The investigator must verify the correctness of the data entered by the site by electronically dating and signing the eCRF. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require re-signature by the investigator. The person making the change to the data, and the date, time, and reason for the change will be identified in the audit trail.

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

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

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

Statistical programming standards
CDISC controlled terminology version 06-Nov-2020 or newer was used for definition of controlled terminology throughout this protocol. Latest version of standard data tabulation model (SDTM) available at FSFV will be used for data.

Archiving of trial documentation

The investigator at each trial site must make arrangements to store the essential trial documents, including the investigator trial file [55]. Essential trial documents must be stored until LEO Pharma informs the investigator that the documents are no longer to be retained, or longer if required by local regulations.

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

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

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

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

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

Appendix 3E: Registration, reporting, and publication policy

Trial disclosure

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

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

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

Publications

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

A publication will be submitted for publication within 12 months after the clinical trial has been completed or terminated at the trial site and all data have been received, defined as final database lock of the clinical trial. 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.

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 [43].

Appendix 3F: Insurance

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

Appendix 3G: Financial disclosure

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

Appendix 3H: Committee structure

Not applicable.

Appendix 3I: Trial and trial site closure

Premature termination of trial or trial site

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

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

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

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

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

Completion of trial

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

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

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

Appendix 3J: Responsibilities

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

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

Appendix 4: Country-specific requirements

Not applicable

Appendix 5: Short version and justification for eligibility criteria

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

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

Exclusion criteria		
No.	**Short version**	**Justification**
1	Treatment with systemic immunosuppressive/immunomodulating medication (excluding systemic antihistamines if taken at stable dose already before baseline) e.g JAK inhibitors, immunoglobulin/blood products within 2 weeks or 5 half-lives prior to baseline, whichever is longer.	To not interfere with primary endpoint and efficacy assessments.
2	Treatment with systemic corticosteroids within 4 weeks prior to baseline	To not interfere with primary endpoint and efficacy assessments
3	Intake of nonsteroidal anti-inflammatory drugs (NSAIDs) within 1 week prior to baseline. Intake of paracetamol will be allowed.	To not interfere with primary endpoint and efficacy assessments
4	Treatment with biologics within 5 half-lives (if known) or 16 weeks prior to baseline, whichever is longer.	To not interfere with primary endpoint and efficacy assessments
5	Allergen immunotherapy within 4 weeks prior to baseline	To not interfere with primary endpoint and efficacy assessments
6	Treatment with TCS, TCI, topical PDE-4 inhibitor, or other topical prescription treatments within 1 week prior to baseline.	To not interfere with primary endpoint and efficacy assessments
7	Use of tanning beds or phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]) within 4 weeks prior to baseline	To not interfere with efficacy assessments

8	Treatment with a live (attenuated) vaccine within 12 weeks prior to baseline.	To ensure safety of subjects as LEO 138559 could potentially interact with this.
9	Active dermatologic condition that could confound the diagnosis of AD or interfere with assessment of the treatment.	To exclude conditions that are likely to interfere with the assessment of severity of AD.
10	History of malignancy within 5 years prior to randomization, apart from nonmetastatic BCC, SCC of the skin, or cervical carcinoma in-situ, considered cured by the standard of care.	To ensure safety of subjects.
11	Clinically significant active chronic or acute infection requiring systemic treatment within 4 weeks prior to baseline that may compromise the safety of the subject	To ensure safety of subjects
12	Skin infection within 1 week prior to the baseline visit.	To ensure safety of subjects
13	Current or recent (within 2 years prior to baseline) gastrointestinal ulcers	To ensure safety of subjects
14	History of any of the following: anaphylaxis, immune complex disease, pancreatic disease, inflammatory bowel disease or known or suspected history of immunosuppressive disorder	Anaphylaxis: To ensure safety of subjects given the potential increased risk of anaphylaxis and serious allergic reactions after administration of foreign proteins. Immune complex disease: To ensure safety of subjects given the potential increased risk that antibody-antigen complexes can accumulate and cause a Type III allergic reaction. Pancreatic disease: To ensure safety of subjects given the potential increased risk of impaired wound healing of pancreas with LEO 138559. Inflammatory bowel disease: To ensure safety of subjects given the potential increased risk of impaired wound healing of intestine with LEO 138559.

		Known or suspected history of immunosuppressive disorder: To ensure safety of subjects given the potential increased risk of infections of the skin, lung, and intestines with LEO 138559s
15	Known or suspected hypersensitivity to any component(s) of the IMPs	To ensure safety of subjects
16	Known or suspected hypersensitivity to local anesthetics	To ensure safety of subjects
17	Presence of hepatitis B or C infection at screening. These are defined as: 1) Positive hepatitis C Ab, or 2) Positive HBsAg, or 3) Negative anti-HBs Ab AND positive anti-HBc Ab	To ensure safety of subjects
18	History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening	To ensure safety of subjects
19	Subject has a positive or indeterminate *Mycobacterium tuberculosis* IFN-γ release assay test or a positive purified protein derivative (PPD) test at screening	To ensure safety of subjects given the potential increased risk of infections of the lung with LEO 138559.
20	Current diagnosis of diabetes.	To ensure safety of subjects by decreasing the risk of enrolling subjects who may be at increased risk of severe COVID-19 infection.
21	Clinically significant abnormalities detected on vital signs or ECG (apart from 1st degree atrioventricular (AV) block that is allowed	To ensure safety of subjects
22	Serious heart conditions (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and/or pulmonary hypertension).	To ensure safety of subjects by decreasing the risk of enrolling subjects who may be at increased risk of severe COVID-19 infection.
23	Chronic lung diseases (e.g., chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and/or cystic fibrosis)	To ensure safety of subjects by decreasing the risk of enrolling subjects who may be at increased risk of severe COVID-19 infection.
24	Acute asthma, acute bronchospasm, moderate to severe asthma [as defined by GINA guidelines]	To ensure safety of subjects by decreasing the risk of enrolling subjects who may be at increased risk of severe COVID-19 infection.

25	Obesity (BMI ≥35)	To ensure safety of subjects by decreasing the risk of enrolling subjects who may be at increased risk of severe COVID-19 infection.
26	Subject has laboratory abnormalities that, in the opinion of the investigator, will prevent the subject from completing the trial or interfere with the analysis of results	To ensure safety of subjects
27	Subject is pregnant or lactating	For the safety of the unborn/newborn child.
28	Subject has a history of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.	To ensure safety of the subjects, and integrity and validity of the trial data.
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.	To ensure integrity of trial data.
30	Any disorder at screening and/or baseline, which is not stable in the opinion of the investigator	To ensure safety of the subjects, and integrity and validity of the trial data.
31	Any significant abnormal finding at baseline and/or screening which may in the opinion of the investigator	To ensure safety of the subjects, and integrity and validity of the trial data.
32	Treatment with any non-marketed drug substance within the last 4 weeks or 5 half-lives prior to baseline, whichever is longer.	To ensure safety of subjects and ensure lack of confounding of measurements (e.g. efficacy, PK, and PD).
33	Current participation in any other interventional clinical trial.	To ensure safety of subjects and ensure lack of confounding of measurements (e.g. efficacy, PK, and PD).
34	Previously randomised in this clinical trial.	To ensure integrity and validity of the trial data due to the possibility of duplicate subject entries.
35	Subjects who are legally institutionalised.	To ensure compliance with Declaration of Helsinki [37].

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

Assoc.-Prof. PD Patrick M. Brunner, MD, MSc
Department of Dermatology
Medical University of Vienna
Währinger Gürtel 18-20
1090 Vienna
Austria

Appendix 7: Protocol Amendment history

Amendment 1 (08-Mar-2022)

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

Overall rationale for the amendment:

The Clinical Trial Protocol Version 2.0 became necessary in order to take account of objections raised by the Ethics Committee (EC) of the Medical University of Vienna **(**Ethikkommission der Medizinischen Universität Wien) the relevant Austrian Ethics Committee (EC) received on 22-Feb-2022.

Section no. and name	**Description of change**	**Brief rationale**
Synopsis 8.2 Exclusion criteria 9.7 Prohibited medications and procedures Appendix 5	Exclusion criterion #1 has been modified, shortening the wash-out period for the treatment with systemic immunosuppressive/immunomodulating medication from **4 weeks to only 2 weeks**. The information on the length of the washout period for treatment with systemic immunosuppressive / immunomodulatory drugs was also adjusted in Panel 5 (Prohibited medication(s) and/or procedure(s)). Short version of eligibility criteria was updated accordingly.	Based on the limited data available for LEO 138559, the EC requested to add another inclusion criterion that only allows the inclusion of patients on systemic therapy who have not responded adequately to a conventional systemic therapy. As the original protocol already intended to only include patients who either qualify for systemic therapy or who have already failed to respond adequately to conventional local and systemic therapies (refer to inclusion criterion #4), no new inclusion criterion have been added. Nonetheless, as a wash-out period of 4 weeks in patients with prior unsuccessful Janus kinase inhibitor or ciclosporin A therapy seems to be very long in relation to their short half-life's (half-life 10-16 hours) the wash-out period for these therapies is shortened to only 2 weeks or to 5x the half-life, whichever is longer, to avoid any unnecessary withhold.
Synopsis	Exclusion criterion #14 has been changed by taking out the history of	Furthermore, the EC requested to clarify, if it is intended to

Section no. and name	**Description of change**	**Brief rationale**
8.2 Exclusion criteria Appendix 5	zoster infection and viral skin infections. Short version of eligibility criteria was in addition updated accordingly.	exclude patients with a history of viral skin infections. As this is neither intended nor necessary, the respective exclusion criterion (No. #14) has been adapted accordingly.
Section 11.10	As no biobanking is planned the respective phrase in section 11.10, inserted by mistake, has been deleted.	The Ethics Committee has also objected that the information on whether a biobank is planned remains unclear in the protocol. In fact, no biobank is planned. All biological samples collected will only be used according to the investigations outlined in the protocol and will be destroyed afterwards.
Clinical trial protocol statements	Per Sørensen has been replaced by Kyle Raymond, the new lead statistician at LEO Pharma A/S	As the lead statistician has changed, the signatory page needed to be updated
Whole trial protocol	Individual corrections throughout the protocol can be traced back via the track change mode and are not listed here.	Mistakes, such as typos or incorrect cross-references that were noticed during the review of this protocol amendment, were corrected in order to be as unambiguous and precise as possible

Amendment 2 (14-Apr-2022)

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

Overall rationale for the amendment:

With the introduction of COVID-19 vaccines, COVID-19 may now be considered more like other influenza-like diseases – and COVID-19 (confirmed by a positive SARS-CoV-2 test result) is no longer deemed a major health risk as disease symptoms are commonly only mild and patients rapidly recover from COVID-19. This amendment is intended to take account for the changed status of the COVID-19 pandemic.

Section no. and name	**Description of change**	**Brief rationale**
10.2.1 Reasons for permanent discontinuation of IMP	Rewording of the reason for permanent discontinuation of IMP due to SARS-CoV-2 infection <u>Formerly:</u> Subjects will permanently discontinue IMP in the event of: • …. • Infection with SARS-CoV-2 (COVID -19). • …. <u>New:</u> Subjects will permanently discontinue IMP in the event of: • …. • Symptomatic infection with SARS-CoV-2 that is likely to have an impact on efficacy or safety data (i.e., patients with a SARS-CoV-2 infection without or very mild symptoms only (e.g., rhinitis or sore throat) might continue with the study at investigator's	The adjustment was made in the light of the changing course of disease in case of infection with SARS-CoV-2, which currently tends to show milder courses and shorter durations due to the vaccination status but also the dominant viral variant. It is important to note the investigational drug is not believed to present a risk of a decreased antiviral immunity in subjects infected with SARS-CoV-2. In addition, it is not believed that the investigational drug increase the susceptibility of a subject to contract COVID-19 or other infections. The infection situation will continue to be monitored and necessary adjustments will be implemented as needed.

Section no. and name	**Description of change**	**Brief rationale**
	discretion and in accordance with the applicable local regulations). • ….	
Clinical trial protocol statements	PPD has been replaced by PPD as Senior Director, Medical Department at LEO Pharma A/S	Due to personnel changes and changes in project responsibility at LEO Pharma A/S, it is necessary to adapt the Approval Statement accordingly