Dermatology beyond the skin

Cover Page

Official title: A phase 2b, double-blind, randomised, 5-arm, vehicle-controlled, dose-ranging trial to evaluate the efficacy and safety of twice daily topical applications of delgocitinib cream 1, 3, 8, 20 mg/g for 8 weeks in adult subjects with mild to severe atopic dermatitis
LEO Pharma number: LP0133-1275
NCT number: NCT03725722
Date: 22-Aug-2019

Updated Clinical Trial Protocol

LP0133-1275

Phase 2b dose-ranging trial to evaluate delgocitinib cream 1, 3, 8, and 20 mg/g compared to delgocitinib cream vehicle over an 8-week treatment period in adult subjects with atopic dermatitis

Phase 2b – dose-ranging trial

A phase 2b, double-blind, randomised, 5-arm, vehicle-controlled, dose-ranging trial to evaluate the efficacy and safety of twice daily topical applications of delgocitinib cream 1, 3, 8, 20 mg/g for 8 weeks in adult subjects with mild to severe atopic dermatitis

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:**	**LP0133-1275**
	Date:	**22-Aug-2019**
	EudraCT no:	**Not applicable**
	Version:	**3.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

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

PDD , MSc Stat
Biostatistics Lead, Global Clinical Operations

PDD , MD
Vice President, Medical Sciences

PDD MA
Clinical Operations Lead, Global Clinical Operations

Approval statement signatory investigator

The signatory investigator approves the clinical trial protocol by manually signing the Signatory Investigator Clinical Trial Protocol Approval Form, which is a separate document appended to this document.

The following person has approved this clinical trial protocol:

PDD , MD, PhD, MPH
Signatory investigator

Acknowledgement statement investigators

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

Protocol amendment summary of changes tables

Document	Protocol version	Date	Type of protocol amendment
Amendment 2 (substantial)	3.0	22-Aug-2019	Global
Amendment 1 (substantial)	2.0	09-Jan-2019	Global
Original protocol	1.0	22-Jun-2018	Not applicable

A protocol amendment summary of changes table for the previous amendment is provided in Appendix 7.

Amendment 2 (22-Aug-2019)

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

Overall rationale for the amendment

The main reason for the amendment is to remove the recruitment cap for the number of subjects within each disease severity group due to slow recruitment of subjects with severe atopic dermatitis. Miscellaneous other changes/updates have also been implemented.

The table below summarises changes made in each section and a brief rationale for each change.

Section no. and name	Description of change	Brief rationale
Section 1 Protocol synopsis Section 7.1 Overall trial design Section 7.2	Recruitment cap removed for the number of subjects within each disease severity group.	Capping removed due to slow recruitment of subjects with severe atopic dermatitis. Capping for subjects with mild disease severity was therefore considered superfluous,

Number of subjects needed Section 8.4 Screening and screening failures Section 9.3 Treatment assignment Section 12 Scientific rationale for trial design and appropriateness of assessments Appendix 3D Record keeping, quality control, and data handling		which resulted in the removal of the limit of the number of subjects with moderate disease severity.
Section 14.2 Trial analysis sets	All subjects exposed to IMP will be included in the full analysis set. Per protocol analysis set and safety analysis set updated to reflect the change in the full analysis set.	Randomised subjects not exposed to IMP will not be included in the full analysis set. No bias is introduced by excluding subjects, as this is a blinded trial.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore not summarised.

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List of abbreviations

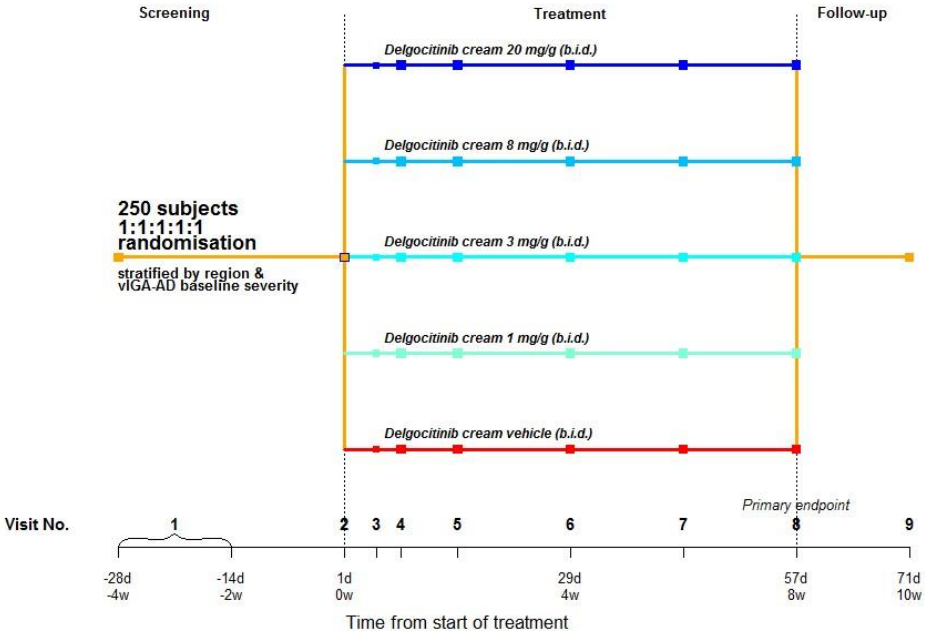
AD	Atopic dermatitis
ADSD	Atopic dermatitis symptom diary
AE	Adverse event
AS	Area score
AUC	Area under the curve
b.i.d.	Twice daily
BSA	Body surface area
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CMO	Contract manufacturing organisation
CONSORT	Consolidated Standards of Reporting Trials
CRA	Clinical research associate
CRO	Contract research organisation
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical trial report
D	Day
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI50	At least 50% reduction in EASI score
EASI75	At least 75% reduction in EASI score
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
EMA	European Medicines Agency
ePRO	Electronic patient-reported outcome
EQ-5D-5L	EuroQoL 5-Dimension Health Questionnaire 5 Level
FDA	Unites States Food and Drug Administration
GCP	Good Clinical Practice
HBcAb	Hepatitis B core antibody
HBsAB	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus

HDL	High density lipoprotein
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IC_{50}	Half maximum inhibitory concentration
ID	Identification number
IEC	Independent ethics committee
IgE	Immunoglobulin E
IL	Interleukin
IMP	Investigational medicinal product
IND	Investigational new drug
INN	International non-proprietary name
IRB	Institutional review board
IRT	Interactive response technology
JAK	Janus kinase
LDL	Low density lipoprotein
LEO	LEO Pharma A/S
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measurements
NBUVB	Narrow band ultraviolet B
NRS	Numeric rating scale
PDE-4	Phosphodiesterase-4
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
POEM	Patient-Oriented Eczema Measure
PRO	Patient-reported outcome
PT	Preferred term
PUVA	Psoralen and ultraviolet A
S. aureus	*Staphylococcus aureus*
SAE	Serious adverse event
SCORAD	Scoring Atopic Dermatitis

SCORAD50	At least 50% reduction in SCORAD
SCORAD75	At least 75% reduction in SCORAD
SDTM	Study data tabulation model
SF-36	36-item Short Form Health Survey
SOC	System organ class
SUSAR	Serious and unexpected suspected adverse reaction
SS	Severity score
STAT	Signal transducer and activator
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid
Th	T helper cell
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal range
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
vIGA-AD™	Validated Investigator Global Assessment scale for Atopic Dermatitis (termed vIGA-AD in this protocol)
vIGA-AD TS	vIGA-AD treatment success, i.e. a vIGA-AD score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement
W	Week
WHO	World Health Organization
WLQ	Work Limitation Questionnaire

1 Protocol synopsis

Trial ID IND no. NCT no.	Trial ID: LP0133-1275. IND no: CCI [redacted] NCT03725722
Title of trial	A phase 2b, double-blind, randomised, 5-arm, vehicle-controlled, dose-ranging trial to evaluate the efficacy and safety of twice daily topical applications of delgocitinib cream 1, 3, 8, 20 mg/g for 8 weeks in adult subjects with mild to severe atopic dermatitis.
Short title of trial	Phase 2b dose-ranging trial to evaluate delgocitinib cream 1, 3, 8, and 20 mg/g compared to delgocitinib cream vehicle over an 8-week treatment period in adult subjects with atopic dermatitis.
Main objectives	Primary objective: To establish the dose-response relationship of twice daily applications of delgocitinib cream 1, 3, 8 and 20 mg/g and delgocitinib cream vehicle for 8 weeks in the treatment of subjects with mild to severe AD. Other objectives: To compare the safety of twice daily applications of delgocitinib cream 1, 3, 8, 20 mg/g with delgocitinib cream vehicle for 8 weeks in the treatment of subjects with mild to severe AD. To evaluate the health-related quality of life and efficacy of twice daily applications of delgocitinib cream 1, 3, 8, 20 mg/g and delgocitinib cream vehicle for 8 weeks in the treatment of subjects with mild to severe AD. To evaluate the effect of delgocitinib on *S. aureus* colonisation of the skin, skin microbiome, and skin inflammation.
Primary endpoint	• Change from baseline to Week 8 in Eczema Area and Severity Index (EASI) score.
Secondary endpoints	• Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD) score of 0 (clear) or 1 (almost clear) with ≥2-step improvement (vIGA-AD treatment success [TS]) from baseline to Week 8. • EASI75 at Week 8. • Time to vIGA-AD TS.
Final collection of data for the primary endpoint	Week 8.
Trial design	The trial is designed as a double-blind, multi-centre, randomised, 5-arm, vehicle-controlled, parallel-group trial in which adult subjects with mild to severe AD will be treated with delgocitinib cream (1, 3, 8, 20 mg/g) or delgocitinib cream vehicle for 8 weeks. The trial consists of a screening period, a treatment period, and a follow-up period.

	Screening period The screening period has a minimum duration of 2 weeks and a maximum duration of 4 weeks. At the screening visit, the subjects' eligibility to enter the trial will be checked. The subjects will receive training in completion of an electronic diary (eDiary). Furthermore, the subjects will be asked to fill out patient-reported outcome measures (PROs). Treatment period At baseline (Day 1), subjects' eligibility to enter the trial will be confirmed and, if still eligible, the subjects will be randomised to 1 of the 5 treatment groups. The randomisation will be stratified by the severity of AD according to vIGA-AD (mild, moderate, and severe) and region (North America and Australia). The first application of the investigational medicinal product (IMP) will occur at the trial site at baseline (Day 1). The subsequent IMP applications will be performed by the subjects at home twice daily for 8 weeks. During the treatment period, the subjects will be required to return to the trial site for the visits scheduled at Weeks 1, 2, 4, 6 and 8. The last IMP application will occur before the subjects attend the visit scheduled at Week 8. Follow-up period All subjects will attend a follow-up visit approximately 2 weeks after the last IMP application for assessment of safety. 

Main assessments	Investigator efficacy assessments:

	• EASI for assessment of severity and extent of AD. • vIGA-AD for assessment of the subject's global disease severity. • Scoring Atopic Dermatitis (SCORAD) for evaluation of the extent and severity of AD lesions, along with subjective symptoms. <u>Subject assessments of efficacy and health-related quality of life; PROs:</u> • Atopic Dermatitis Symptom Diary (ADSD). • Eczema-related Sleep Numeric Rating Scale (Eczema-related Sleep NRS). • Patient-Oriented Eczema Measure (POEM). • Dermatology Life Quality Index (DLQI). • Patient Global Impression of Severity (PGI-S). • Patient Global Impression of Change (PGI-C). • 36-item Short Form Health Survey (SF-36). • EuroQoL 5-Dimension Health Questionnaire 5 Level (EQ-5D-5L). • Work Limitation Questionnaire (WLQ). • Treatment Satisfaction Questionnaire for Medicine (TSQM). <u>Safety assessments:</u> • Vital signs, physical examination, electrocardiograms, laboratory testing, subject assessment of local tolerability, and adverse events reporting.
Main criteria for inclusion	• Age 18 years and above. • Diagnosis of AD as defined by the Hanifin and Rajka 1980 criteria for AD. • History of AD for ≥1 year. • AD involvement of 5–50% treatable body surface area at screening and at baseline (excluding scalp). • Disease severity graded as mild to severe according to vIGA-AD (i.e. vIGA-AD ≥2) at screening and baseline. • Able and willing to follow trial procedures including application of IMP to all AD lesions.
Main criteria for exclusion	• AD lesion(s) on scalp at screening and/or baseline. • Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, rosacea, urticaria, or psoriasis. • Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD. • Use of tanning beds or phototherapy (narrow band ultraviolet B (NBUVB), ultraviolet B (UVB), ultraviolet A1 (UVA1), psoralen and ultraviolet A (PUVA)) within 4 weeks prior to baseline. • Treatment with the following medications within 4 weeks prior to baseline: o Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine, azathioprine, mycophenolate-mofetil, Janus kinase inhibitors, retinoids).

	○ Systemic corticosteroid use (excludes inhaled or intranasal delivery). ○ Three or more bleach baths during any week within the 4 weeks. • Treatment with the following medications within 2 weeks prior to baseline ○ Topical corticosteroids (TCSs). ○ Topical calcineurin inhibitors (TCIs). ○ Topical phosphodiesterase-4 (PDE-4) inhibitors. ○ Oral antibiotics. • Change in systemic antihistamine therapy within 2 weeks prior to baseline i.e. the subjects must not start antihistamine treatment or change the current dosage regime within 2 weeks prior to baseline. • Receipt of live attenuated vaccines 30 days prior to baseline and during the trial including the safety follow-up period. • Receipt of blood products within 4 weeks prior to screening. • Treatment with any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE or dupilumab). ○ Any cell-depleting agents including but not limited to rituximab: within 6 months prior to baseline, or until lymphocyte count returns to normal, whichever is longer. ○ Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline. • History of any active skin infection within 1 week prior to baseline. • A helminth parasitic infection within 6 months prior to screening that has not been treated with, or has failed to respond to, standard of care therapy. • Clinically significant infection within 4 weeks prior to baseline which, in the opinion of the investigator, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial. Clinically significant infections are defined as: ○ A systemic infection. ○ A serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication. • Tuberculosis requiring treatment within the 12 months prior to screening and/or subjects with a positive blood test for tuberculosis at screening*. * Subjects with high risk of latent tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested. • History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at screening, or the

	subject taking antiretroviral medications as determined by medical history and/or subject's verbal report. • Any disorder, including but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, psychiatric, or major physical impairment that is not stable, in the opinion of the investigator, and could: o Affect the safety of the subject throughout the trial. o Influence the findings of the trial or their interpretations. o Impede the subject's ability to complete the entire duration of trial. • Positive hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) or hepatitis C virus (anti-HCV) serology at screening. Subjects with positive HBsAb may be randomised provided they are hepatitis B vaccinated and have negative HBsAg and HBcAb.
Investigational medicinal products	Name of IMP: delgocitinib cream. Active substance: delgocitinib. Formulation: cream. Formulation strength: 1, 3, 8, and 20 mg/g and vehicle. Dose and method of administration: twice daily topical application.
Duration of treatment	An 8-week treatment period.
Number of subjects	A total of 250 subjects eligible subjects will be randomised 1:1:1:1:1 to delgocitinib cream 1, 3, 8, 20 mg/g or delgocitinib cream vehicle.
Number and distribution of trial sites	Approximately 25 sites in North America (US and Canada) and Australia.
Statistical methods	A dose-response modelling approach will be applied for the primary endpoint, change from baseline to Week 8 in EASI, and the secondary endpoints, EASI75 and vIGA-AD TS. The dose-response relationship will be modelled by 3 identified candidate models selected based on the expected dose-response relationship for delgocitinib cream. In addition, continuous endpoints will be analysed using a repeated measurements model and for the binary endpoints, the difference in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test. For the primary and secondary endpoints, the selection of the dose-response model that fits data best will be controlled using a family-wise error rate of 5%. There will be no adjustment for the multiple testing of primary and secondary endpoints, all p-values will be considered nominal.
Signatory investigator	PDD , MD, PhD, MPH

	Northwestern University, Department of Dermatology, Chicago, Illinois, USA (until 30-Sep-2019). George Washington University, Department of Dermatology, Washington DC, USA (from 01-Oct-2019).
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark.

2 Trial identification

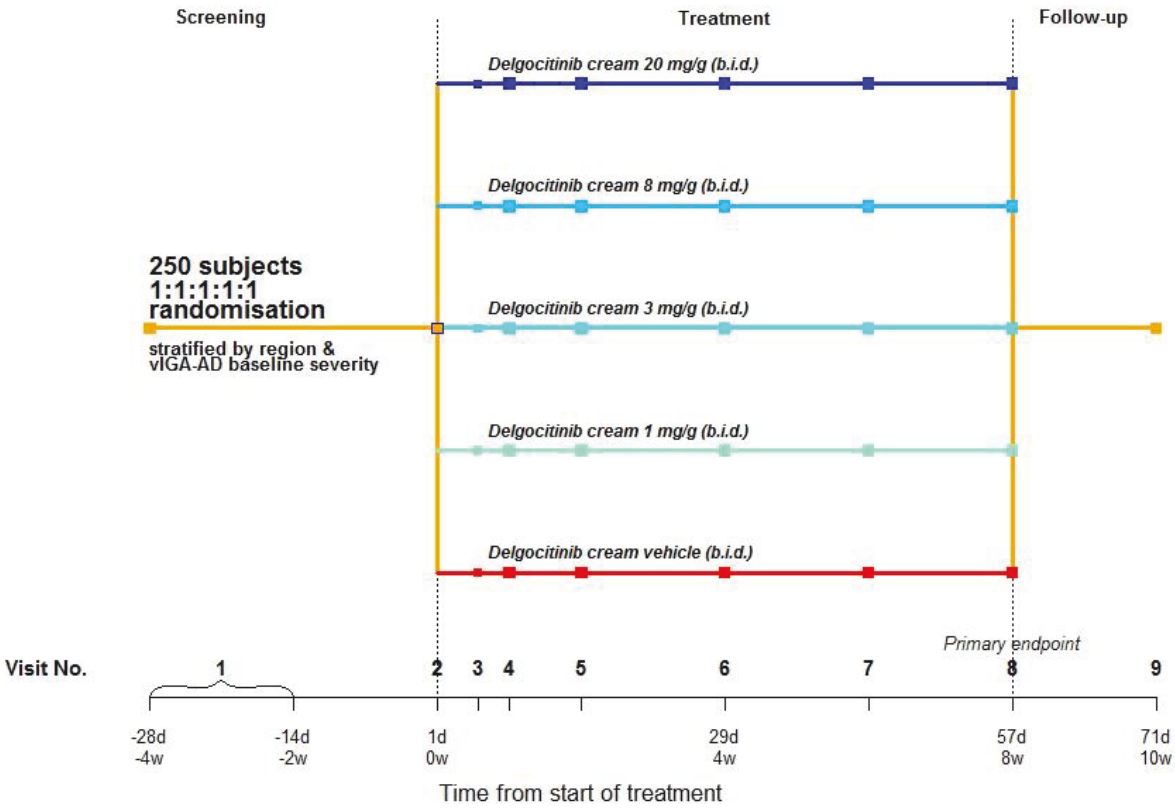
IND number: CCI

NCT number: NCT03725722

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

3 Schematic of trial design

Panel 1: Trial design



Abbreviations: vIGA-AD: Validated Investigator Global Assessment scale for Atopic Dermatitis; b.i.d: twice daily; w: week; d: day

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

	Screening[a]	Treatment period						End of treatment/ early termination	Follow-up[e]	Primary endpoint visit at Week 8, if applicable[f]	Unscheduled visit, if applicable[g]	References (protocol sections)
Visit	**1**	**2**	**3[c]**	**4**	**5**	**6**	**7**	**8[d]**	**9**			
Week	**-4 to -2**	**0**		**1**	**2**	**4**	**6**	**8**	**10**			
Day	**-28 to -14**	**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**			
Visit window (days)[b]	-	-	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Trial population and eligibility												
Informed consent(s)[h]	X											Appendix 3B
Subject eligibility	X	X										8.2, 8.3
Trial products and randomisation												
Randomisation		X										9.3
Dispense IMP		X		X	X	X	X				(X)	9.2
Instruction of IMP application		X										9.2
Application of IMP		Twice daily										9.2
Treatment compliance			X	X	X	X	X	X				9.8.3, 9.8.4
Return of IMP and accountability[i]				X	X	X	X	X				9.8.3
Concomitant medication/concurrent procedures[j]	X	X	X	X	X	X	X	X	X	X	(X)	9.6

	Screening[a]	Treatment period						End of treatment/early termination	Follow-up[e]	Primary endpoint visit at Week 8, if applicable[f]	Unscheduled visit, if applicable[g]	References (protocol sections)
Visit	**1**	**2**	**3[c]**	**4**	**5**	**6**	**7**	**8[d]**	**9**			
Week	**-4 to -2**	**0**		**1**	**2**	**4**	**6**	**8**	**10**			
Day	**-28 to -14**	**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**			
Visit window (days)[b]	-	-	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Investigator assessments at screening/baseline only												
Demographics	X											11.2.1
Fitzpatrick skin type	X											11.2.2
Medical history[k]	X	X										11.2.3
Height and weight		X										11.2.4
BSA involvement[l]	X	X										11.2.5
eDiary hand out/training	X											7.1
Subject assessment of efficacy and health-related quality of life - daily												
eDiary completion: ADSD and Eczema-related Sleep NRS[m]	Daily											11.7.1.1, 11.7.1.2
Subject assessment of efficacy and health-related quality of life – during trial visits												
POEM	X	X		X	X	X	X	X				11.7.1.3
DLQI	X	X		X	X	X	X	X				11.7.1.4
PGI-S	X	X		X	X	X	X	X				11.7.1.5
PGI-C					X	X		X				11.7.1.6
SF-36	X	X		X	X	X	X	X				11.7.1.7
EQ-5D-5L	X	X		X	X	X	X	X				11.7.1.8

	Screening[a]	Treatment period						End of treatment/early termination	Follow-up[e]	Primary endpoint visit at Week 8, if applicable[f]	Unscheduled visit, if applicable[g]	References (protocol sections)
Visit	**1**	**2**	**3[c]**	**4**	**5**	**6**	**7**	**8[d]**	**9**			
Week	**-4 to -2**	**0**		**1**	**2**	**4**	**6**	**8**	**10**			
Day	**-28 to -14**	**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**			
Visit window (days)[b]	-	-	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
WLQ[n]	X	X				X		X				11.7.1.9
TSQM						X		X				11.7.1.10
Investigator assessment of efficacy												
EASI	X	X		X	X	X	X	X		X		11.3.1
vIGA-AD	X	X		X	X	X	X	X		X		11.3.2
SCORAD	X	X		X	X	X	X	X		X		11.3.3
Investigator assessment of safety												
Vital signs	X	X		X	X	X	X	X			(X)	11.4.1
Physical examination	X	X						X			(X)	11.4.2
ECG	X	X						X			(X)	11.4.3
Chemistry, haematology[o]	X	X			X	X		X			(X)	11.4.4
Serology, total IgE, tuberculosis test[p]	X											11.4.4
Serum pregnancy test[q]	X										(X)	11.4.4
Urine pregnancy test[q]		X				X		X			(X)	11.4.4
	Screening[a]	**Treatment period**										

								End of treatment/early termination	**Follow-up[e]**	**Primary endpoint visit at Week 8, if applicable[f]**	**Unscheduled visit, if applicable[g]**	**References (protocol sections)**
Visit	**1**	**2**	**3[c]**	**4**	**5**	**6**	**7**	**8[d]**	**9**			
Week	**-4 to -2**	**0**		**1**	**2**	**4**	**6**	**8**	**10**			
Day	**-28 to -14**	**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**			
Visit window (days)[b]	-	-	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Urinalysis - dipstick	X	X				X					(X)	11.4.4
AEs/SAEs	X	X	X[r]	X	X	X	X	X	X	X	X	13
Subject assessment of local tolerability			X	X	X	X	X	X			X	11.4.5
Other assessments												
PK blood sample				X[s]								11.5.1
Skin swabs/skin microbiome		X						X				11.6.2
Skin biopsy and photography (***optional***)		X[t]		X[u]				X[u,v]				11.6.3
Check skin biopsy wound healing/suture removal			X		X				X			11.6.3
New AD lesions			X	X	X	X	X	X		X	X	11.7.2
Return of eDiary								X				11.7.1
End of trial form[w]								X	X	X		10.3, 11.9

a) All subjects must use an emollient twice daily (or more, as needed) for at least 14 days before randomisation; the background treatment should preferably be an additive free, basic bland emollient

b) If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to baseline/randomisation at Day 1

c) A visit at the trial site is not required on Day 4, a member of trial site personnel will call the subjects
d) End of treatment assessments will be conducted at Week 8. Early termination: subjects, who discontinue IMP treatment prior to Week 8 or withdraw from trial will be asked to return to the trial site for end of treatment assessments at an early termination visit as soon as possible after the last IMP application for completion of all trial procedures scheduled for the visit at Week 8 (except for the skin biopsy, if the subject has consented to have skin biopsies obtained), and they will also be asked to return to the trial site 2 weeks after the last IMP application for a follow-up visit and at Week 8 for a primary endpoint visit
e) All subjects will be asked to return to the trial site approximately 2 weeks after the last IMP application for assessment of safety at a follow-up visit
f) Subjects who discontinue IMP treatment prior to Week 8 will be asked to return to the trial site at Week 8 for a primary endpoint visit
g) Unscheduled visits may occur if subjects need to make a visit in between the scheduled visit dates due to an AE, difficulty complying with the trial protocol requirements, or a significant change in their disease state
h) The informed consent form(s) must be signed prior to performing any protocol related procedures, including but not limited to screening evaluations and alteration of ongoing treatments unless medically justified
i) All returned IMP tubes will be weighed by the CMO
j) Relevant prior/concomitant medication should be included from 6 months prior to Day 1 (baseline) until end of trial
k) Relevant medical history must be recorded from the subject's birth. In case medical history is incomplete at screening visit, missing data will be retrieved at Day 1 (baseline)
l) BSA is assessed as a part of SCORAD
m) Completion of the eDiary will be initiated at the latest 1 week prior to Day 1 (baseline). Compliance with the eDiary completion will be reviewed by the trial site staff throughout the trial.
n) Only for subjects with a paid job.
o) Subjects do not have to be fasting for safety laboratory samples
p) Subjects with high risk of latent tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested
q) For women of childbearing potential, a serum pregnancy test must be performed at the screening visit, and a urine pregnancy test at Day 1 (baseline), Weeks 4 and 8 (end of treatment)
r) If a subject reports an AE, it is up to the investigator's discretion to perform an unscheduled visit
s) Collection of 1 PK plasma sample 2–6 hours after the morning application of IMP. Plasma sample should be collected from a non-treated area.
t) The skin biopsy sampling and the recommended photography scheduled at Day 1 (baseline) must be obtained prior to the first IMP application. This should be done both on lesional and corresponding non-lesional skin if possible
u) The skin biopsy sampling scheduled at Week 1 and Week 8 should be done on lesional skin only
v) The skin biopsy scheduled at Week 8 will be obtained 2–12 hours after the last IMP application. If a subject discontinues IMP treatment prematurely or withdraws from the trial, the skin biopsy scheduled at Week 8 does not have to be obtained

w) An end of trial form must be completed for all subjects, including subjects who discontinue IMP treatment prematurely or withdraw from the trial, at their last trial visit (the early termination visit, the safety follow-up visit, or the primary endpoint visit, whichever comes last)

Abbreviations: ADSD, atopic dermatitis symptom diary; AE, adverse event; CMO, contract manufacturing organisation; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; EASI, Eczema Area and Severity Index; eDiary, electronic diary; EQ-5D-5L, EuroQoL 5 Dimension Health Questionnaire 5-Level; IgE, immunoglobulin E; IMP, investigational medicinal product; NRS, numeric rating scale; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetics; POEM, Patient-Oriented Eczema Measure; SAE, serious adverse event; SCORAD, SCORing Atopic Dermatitis; SF-36: 36-item Short Form Health Survey; TSQM: Treatment Satisfaction Questionnaire for Medication; vIGA-AD, Validated Investigator Global Assessment scale for Atopic Dermatitis; WLQ, Work Limitation Questionnaire

5 Introduction and trial rationale

5.1 Atopic dermatitis

AD is a chronic inflammatory skin disease that may affect up to 20% of children and up to 10% of adults. AD is characterised by widespread, red, swollen, cracked and weeping lesions with crusting and scaling, and is associated with pruritus and susceptibility to bacterial and viral skin infections (Silverberg & Hanifin 2013, Hanifin & Reed 2007, Bieber 2008, Weidinger & Novak 2016). AD is also associated with a substantial patient burden that typically includes poor quality of life, sleep disturbance and reduction in work productivity (Kiebert et al. 2002).

AD is characterised by an activated Th2 pathway in the skin (Bieber 2008, Bao et al. 2013) and increased expression of Th2 cytokines such as IL-4, IL-5, IL-13, IL-2, IL-31, IL-33, and thymic stromal lymphopoietin (Brunner et al. 2017; Czarnowicki et al. 2017; Ong 2014).

In the immune milieu of AD, the enhancement of Th2 cell proliferation and their release of various cytokines via the JAK-STAT pathway is likely the critical factor for the inflammatory responses in AD. This Th2 immune milieu triggers epidermal cells to release various chemokines, pro-inflammatory cytokines, and angiogenic factors that participate in AD pathophysiology. Similarly, this Th2 immune upregulation could then lead to B cell maturation and plasma cell differentiation, resulting in hypersecretion of IgE. IgE binding to skin mast cells causes histamine release, which further exacerbates AD. Moreover, IL-5 released from this Th2 milieu could activate eosinophils that are attracted to the skin by the eotaxin subfamily, potentially worsening the AD condition. In addition, by means of IL-31, an inducer of pruritus, AD becomes increasingly intensified (Bao et al. 2013).

5.2 Experience with investigational medicinal product

Delgocitinib, recently assigned as the international non-proprietary name (INN) for LEO 124249, is a pan-JAK inhibitor, which blocks various cytokine signalling pathways, and widely suppresses the activation of immune and inflammatory cells such as T cells, B cells, mast cells, and monocytes activated by these cytokines.

JAK is a family of intracellular tyrosine kinases consisting of 4 members, JAK1, JAK2, JAK3, and Tyk2, which can associate directly to the intracellular part of various cytokine receptors in various combinations (Pesu et al. 2005, Murray 2007). After a cytokine binds to its cognate receptor, the relevant JAK members are autophosphorylated, which allows them to phosphorylate one or more STAT protein (STAT1, STAT2, STAT3, STAT4, STAT5A/B, and STAT6). The phosphorylated STAT proteins are in turn translocated to the nucleus where they

initiate transcription leading to promotion of growth and activation of a variety of cells. The JAK family is thus essential for cytokines involved in the pathogenesis of various diseases with an immune-inflammatory component to exhibit their physiological activity. The immune mechanisms in AD are mostly driven by T cells, and JAK inhibitors inhibit signal transduction of many T cell-released cytokines.

In non-clinical studies, delgocitinib blocked JAK family members with IC_{50} values ranging from 2–60 nM in biochemical assays and inhibited activation of T cells, B cells, mast cells, and monocytes induced by various JAK cytokines in cellular assays. Topically administered delgocitinib inhibited inflammation in rat and mouse models of contact dermatitis, where T cells activated by various JAK-dependent cytokines were involved in the pathogenesis. Furthermore, delgocitinib improved the impaired skin barrier function, and reduced IL-31-induced scratching in mice. In a study by Amano et al., it was shown that IL-4 and IL-13 downregulated genes involved in keratinocyte differentiation, that STAT3 and STAT6 are involved in keratinocyte differentiation and chemokine production, respectively, and that topical application of delgocitinib suppressed STAT3 activation and improved skin barrier function (Amano et al. 2015).

So far, the clinical development programme for delgocitinib has been based on an ointment formulation. No clinical trials with the cream formulation have been conducted to date.

A total of 7 clinical trials covering different patient populations/indications have been conducted with delgocitinib ointment: Three phase 1 trials in healthy adult subjects and adult subjects with AD and four phase 2 trials in adult subjects with AD, chronic hand eczema, inverse psoriasis and alopecia areata.

A phase 2b trial in subjects with moderate to severe AD demonstrated a statistically significant and dose-dependent treatment effect of delgocitinib, formulated as an ointment, compared to delgocitinib ointment vehicle in terms of the percent change in the modified EASI score (excluding head/neck region) from baseline to end of the 4-week treatment period. Delgocitinib ointment was well-tolerated with no apparent dose-dependent trends in AEs. No SAEs were reported.

5.3 Trial rationale

This phase 2b trial will be the first clinical trial to investigate the cream formulation in subjects with AD.

The purpose of the trial is to establish a dose-response signal and to evaluate the efficacy and safety of delgocitinib (1, 3, 8 and 20 mg/g) formulated as a cream for topical use, in the treatment of subjects with mild to severe AD. The results from this trial will support further development in phase 3 with regards to e.g. dose selection and treatment duration.

There is a clear unmet need for new treatment options in the treatment of patients suffering from AD. Based on the currently available non-clinical and clinical data, delgocitinib has the potential to become a novel local-acting anti-inflammatory and immunosuppressive agent with skin barrier improving properties (Amano et al. 2015) for topical use in AD. There is a reasonable expectation that delgocitinib in a cream formulation will prove to be an effective and well-tolerated treatment based on the mechanism of action, and thereby facilitate the everyday lives of affected patients.

Delgocitinib was originally developed as an ointment and this formulation has been used in all clinical trials performed so far with topical administration. A cream formulation has now been developed for further clinical development with the main purpose of optimising the skin delivery and increase patient-friendliness. Delgocitinib cream contains a relatively low amount of lipid, which facilitates fast absorption into the skin and leaving the skin less greasy following treatment relative to the ointment.

5.4 Justification for dose

CCI

CCI

CCI

CCI

CCI

CCI

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CCI

This dose-ranging trial will investigate the maximum range available with 4 formulation strengths of delgocitinib cream ranging from 1 to 20 mg/g. The highest strength, 20 mg/g, has been selected as this is the highest possible strength at this stage of the pharmaceutical development. The lowest strength of 1 mg/g has been selected in order to cover a large range

of potential strengths. The formulation strengths are distributed equidistantly on the natural logarithmic scale (rounded to whole numbers 1, 3, 8, and 20 mg/g).

5.5 Ethical considerations

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, the ICH-GCP guidelines, in compliance with the approved protocol, and applicable regulatory requirements.

Risks associated with treatment in this clinical trial (risks of experiencing significant adverse reactions associated with dermal or systemic exposure to delgocitinib) are considered minimal.

The trial design chosen for this efficacy and safety trial with delgocitinib cream is regarded as ethically justified and adherent with ethical requirements. The efficacy and safety of delgocitinib cream will be evaluated in adults suffering from mild to severe AD who may benefit from treatment in the trial. Pregnant or breastfeeding women and women trying to become pregnant will not be enrolled in the trial. Women of childbearing potential must agree to use a highly effective method of contraception to prevent pregnancy during the trial.

Trial subjects will be informed at the screening visit that trial procedures prior to baseline (Day 1) may warrant an alteration of their ongoing concomitant treatments. As applicable for the entire trial, the subjects will be instructed to contact the investigator if their AD worsens significantly.

In accordance with the current version of the ICH-GCP guidelines, qualified medical personnel employed by LEO will be readily available to advise on trial-related medical questions. Medical monitoring will be performed throughout the trial. Safety data will be reviewed regularly by Global Pharmacovigilance at LEO to ensure routine signal detection.

5.6 Benefit/risk assessment

There is an unmet medical need for new topical treatments for use in patients with mild to severe AD as the majority of the current treatment options have associated limitations in terms of efficacy and/or safety.

No important identified risks have been documented during the overall non-clinical and clinical development of delgocitinib to date. A detailed overview of non-clinical and clinical data on delgocitinib is available in the current Investigator’s Brochure.

The risk to subjects in this trial will be minimised by fulfilment of all eligibility criteria and by close clinical monitoring. As stopping current AD treatment during the trial treatment period carries an inherent risk of worsening AD symptoms during the screening period, the subjects will be instructed to contact the investigator if their AD symptoms worsens significantly during this period.

To ensure the safety and well-being of subjects participating in this trial, safety monitoring will be evaluated as described in Section 11.4. The risks associated with the following invasive trial procedures are considered minimal. Blood samples can be considered a low risk procedure. Skin biopsies are optional to the subject. The size of the skin biopsies should not necessitate suturing, but suturing can be performed at the investigator's discretion. The risk associated with a skin biopsy, including secondary infection, is considered low.

Altogether, the risks associated with participating in this clinical trial are considered very low and outweighed by the benefit of a potential future treatment option for AD. There is an opportunity for a positive treatment effect for the subjects participating in this clinical trial based on the currently available clinical data.

6 Trial objectives and endpoints

Panel 3: Objectives and endpoints

Objectives	Endpoints
Primary objective	Primary and secondary endpoints
To establish the dose-response relationship of twice daily applications of delgocitinib cream 1, 3, 8 and 20 mg/g and delgocitinib cream vehicle for 8 weeks in the treatment of subjects with mild to severe AD.	*Primary endpoint* • Change from baseline to Week 8 in EASI score. *Secondary endpoints* • vIGA-AD score of 0 (clear) or 1 (almost clear) with ≥2-step improvement (vIGA-AD TS) from baseline to Week 8. • EASI75 at Week 8. • Time to vIGA-AD TS.
Other objectives	Other endpoints
To compare the safety of twice daily applications of delgocitinib cream 1, 3, 8, 20 mg/g with delgocitinib cream vehicle for 8 weeks in the treatment of subjects with mild to severe AD.	*Safety* • Number of AEs.
To evaluate the health-related quality of life and efficacy of twice daily applications of delgocitinib cream 1, 3, 8, 20 mg/g and delgocitinib cream vehicle for 8 weeks in the treatment of subjects with mild to severe AD.	*Health-related quality of life and efficacy* • EASI50 at Week 8. • EASI90 at Week 8. • SCORAD50 at Week 8. • SCORAD75 at Week 8. • Change in SCORAD from baseline to Week 8. • Change in ADSD (weekly average for each individual symptom) from baseline to Week 8. ○ Reduction in worst pruritus ("itch" – one of the symptoms captured in ADSD) (weekly average) of ≥4 points from baseline to Week 8 among subjects with baseline worst pruritus (weekly average) ≥4. • Change in Eczema-related Sleep NRS (weekly average) from baseline to Week 8. • Reduction in DLQI of ≥4 point from baseline to Week 8 among subjects with baseline DLQI ≥4. • Change in DLQI score from baseline to Week 8. • Change in POEM from baseline to Week 8. • Change in EQ-5D-5L from baseline to Week 8. • TSQM at Week 8. • Change in WLQ from baseline to Week 8.

Objectives	Endpoints
	• Change in SF-36 from baseline to Week 8. *Efficacy over time* • vIGA-AD TS at each scheduled assessment until Week 6. • EASI75 at each scheduled assessment until Week 6. • Change in SCORAD from baseline to each scheduled assessment until Week 6. • Change from baseline to each week from Week 1 to Week 7 in ADSD (weekly average for each individual symptom). o Reduction of worst pruritus (weekly average) of ≥4 points from baseline to each week from Week 1 to Week 7 among subjects with baseline worst pruritus (weekly average) ≥4. • Change from baseline to each week from Week 1 to Week 7 in Eczema-related Sleep NRS (weekly average). • Change in DLQI score from baseline to each scheduled assessment until Week 6. • Reduction in DLQI of ≥4 points from baseline to each scheduled assessment until Week 6 among subjects with baseline DLQI ≥4. *Biomarkers* • Change in *S. aureus* colonisation from baseline to Week 8. • Change in microbiome composition from baseline to Week 8. • Change in expression of genes involved in AD pathogenesis in skin biopsies from baseline to Week 1. • Change in expression of genes involved in AD pathogenesis in skin biopsies from baseline to Week 8.
To evaluate the effect of delgocitinib on *S. aureus* colonisation of the skin, skin microbiome, and skin inflammation.	

Abbreviations: ADSD, atopic dermatitis symptom diary; AE, adverse event; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D-5L, EuroQoL 5 Dimension Health Questionnaire 5-Level; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; SAE, serious adverse event; SCORAD, SCORing Atopic Dermatitis; SF-36: 36-item Short Form Health Survey; TSQM: Treatment Satisfaction Questionnaire for Medication; vIGA-AD, Validated Investigator Global Assessment scale for Atopic Dermatitis; WLQ, Work Limitation Questionnaire

7 Trial design

7.1 Overall trial design

This is a phase 2b double-blind, multi-centre, randomised, 5-arm, vehicle-controlled, parallel-group trial. The trial is designed to establish a dose-response signal and to investigate the efficacy and safety of delgocitinib cream in the treatment of adult subjects with mild to severe AD. The trial design is illustrated in Panel 1.

The trial consists of a screening period, a treatment period and a follow-up period.

Screening period - between 2 and 4 weeks prior to baseline visit (Day 1)

The screening period has a minimum duration of 2 weeks and a maximum duration of 4 weeks.

At the screening visit, the subjects' eligibility to enter the trial will be checked. Trial-specific measurements will be performed as outlined in Section 11.

The subjects will receive training in completion of an eDiary at the screening visit and will be given an electronic device to record certain PROs. Furthermore, to complete training of the eDiary and as an opportunity to fill out PROs before the treatment period, subjects will be asked to complete PROs at the screening visit. Completion of the eDiary will be initiated at the latest 1 week prior to the baseline visit (Day 1).

All subjects must use an emollient twice daily (or more, as needed) for at least 14 days before Day 1; this background treatment should preferably be an additive free, basic bland emollient. After randomisation on Day 1, emollients must not be used concomitantly with delgocitinib cream or delgocitinib cream vehicle on lesional skin. Subjects may however continue to use their background emollient treatment on non-lesional skin throughout the trial (including safety follow-up).

Treatment period - 8 weeks

At baseline (Day 1), subjects' eligibility to enter the trial will be confirmed and, if still eligible, subjects can be randomised 1:1:1:1:1 to one of the following 5 treatment groups in a 1:1:1:1:1 ratio: delgocitinib cream 1, 3, 8, 20 mg/g or delgocitinib cream vehicle.

The subjects will apply the IMP (delgocitinib cream 1, 3, 8, or 20 mg/g or delgocitinib cream vehicle) twice daily for 8 weeks. The first application of the IMP will occur at the trial site on

Day 1 after all baseline assessments have been carried out. The subsequent IMP applications will be performed by the subjects at home.

During the 8-week treatment period, the subjects will return to the trial sites for the visits scheduled at Weeks 1, 2, 4, 6, and 8. On Day 4, a member of trial site personnel will call the subjects to ask them a non-leading question about AEs e.g. “How have you felt since I saw you last?”, and to inquire about compliance with treatment and eDiary completion. The last IMP application will occur at the subjects’ home before the subjects attend the visit scheduled at Week 8. Efficacy and safety assessments during the treatment period will be performed as described in Section 11.

Follow-up period - 2 weeks

All randomised subjects will attend a follow-up visit approximately 2 weeks after the last IMP application for assessment of safety. This visit will mark the end of trial participation for subjects who have completed the entire trial. For subjects who discontinue trial treatment prematurely or withdraw from the trial, please refer to Section 10.3.

7.2 Number of subjects needed

This trial will be conducted at approximately 25 sites in North America and Australia. The anticipated minimum number of randomised subjects per trial site is 6 and the maximum number of subjects per trial site is 30.

Assuming a screening failure rate of approximately 25%, approximately 334 subjects will be screened and approximately 250 subjects will be randomly assigned to trial treatment (50 subjects in each of the 5 treatment groups: delgocitinib cream 1, 3, 8, and 20 mg/g and delgocitinib cream vehicle). The statistical power considerations for this sample size are described in Section 14.1.

The randomisation is stratified by the severity of AD according to vIGA-AD (vIGA-AD score of 2 (mild), 3 (moderate), or 4 (severe)) and region (North America and Australia).

7.3 End of trial definition

A subject is considered to have completed the trial if they have completed all periods of the trial (i.e. screening, treatment and the safety follow-up).

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

Final collection of data for the primary endpoint occurs at Week 8.

7.4 Software

CDISC controlled terminology version 30-Mar-2018 or newer was used for definition of controlled terminology used throughout this protocol and will be used for statistical programming and output. SDTM version 1.4 will be used for data tabulations and SDTM Implementation Guide version 3.2 will be adhered to.

Dose-response modelling will be done using the package DoseFinding implemented in R statistical software version 3.5.0. All other analysis will be performed using SAS® statistical software version 9.4.

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 eCRF if the subject has met all the inclusion criteria and none of the exclusion criteria.

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

8.2 Inclusion criteria

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

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

2. Age 18 years and above.

3. Diagnosis of AD as defined by the Hanifin and Rajka criteria for AD (Hanifin & Rajka 1980, Appendix 6).

4. History of AD for ≥1 year.

5. AD involvement of 5–50% treatable body surface area at screening and at baseline (excluding scalp).

6. Disease severity graded as mild to severe according to vIGA-AD (i.e. vIGA-AD ≥2) at screening and baseline.

7. Able and willing to follow trial procedures including application of IMP to all AD lesions.

8. A woman of childbearing potential* must use a highly effective** form of birth control throughout the trial and at least for 2 weeks after last application of IMP.
   * 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, intrauterine hormone-releasing system, 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), vasectomised partner (given that the subject is monogamous).

8.3 Exclusion criteria

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

1. AD lesion(s) on scalp at screening and/or baseline.
2. Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, rosacea, urticaria, or psoriasis.
3. Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD.
4. Use of tanning beds or phototherapy (NBUVB, UVB, UVA1, PUVA) within 4 weeks prior to baseline.
5. Treatment with the following medications within 4 weeks prior to baseline:
    - Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine, azathioprine, mycophenolate-mofetil, Janus kinase inhibitors, retinoids).
    - Systemic corticosteroids (excludes inhaled or intranasal delivery).
    - Three or more bleach baths during any week within the 4 weeks.
6. Treatment with the following medications within 2 weeks prior to baseline:
    - TCSs.
    - TCIs.
    - Topical PDE-4 inhibitors.

- Oral antibiotics.

7. Change in systemic antihistamine therapy within 2 weeks prior to baseline i.e. the subjects must not start antihistamine treatment or change the current dosage regime within 2 weeks prior to baseline.
8. Receipt of live attenuated vaccines 4 weeks prior to baseline.
9. Receipt of blood products within 4 weeks prior to screening.
10. Treatment with any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE or dupilumab).
    - Any cell-depleting agents including but not limited to rituximab: within 6 months prior to baseline, or until lymphocyte count returns to normal, whichever is longer.
    - Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline.
11. 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 prior to baseline or 5 half-lives, whichever is longer.
12. History of any active skin infection within 1 week prior to baseline.
13. A helminth parasitic infection within 6 months prior to screening that has not been treated with, or has failed to respond to, standard of care therapy.
14. Clinically significant infection within 4 weeks prior to baseline which, in the opinion of the investigator, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial. Clinically significant infections are defined as:
    - A systemic infection.
    - A serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication.
15. Tuberculosis requiring treatment within the 12 months prior to screening and/or subjects with a positive blood test for tuberculosis at screening*.
    * Subjects with high risk of latent tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested.

16. History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.
17. Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.
18. History of cancer:
    - Subjects who have had basal cell carcinoma, localised squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to screening.
    - Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to screening.
19. Any disorder, including but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, psychiatric, or major physical impairment that is not stable, in the opinion of the investigator, and could:
    - Affect the safety of the subject throughout the trial.
    - Influence the findings of the trial or their interpretations.
    - Impede the subject's ability to complete the entire duration of trial.
20. Any abnormal finding which may:
    - Put the subject at risk because of his/her participation in the trial.
    - Influence the results of the trial.
    - Influence the subject's ability to complete entire duration of the trial.

    The abnormal finding must be clinically significant and observed during the screening period. Examples include abnormal findings in physical examination, vital signs, ECG, haematology, clinical chemistry, or urinalysis.
21. Positive HBsAg, HBsAb, HBcAb or anti-HCV serology at screening. Subjects with positive HBsAb may be randomised provided they are hepatitis B vaccinated and have negative HBsAg and HBcAb.

22. Alanine aminotransferase or aspartate aminotransferase level ≥2.0 times the upper limit of normal range at screening.
23. Known or suspected hypersensitivity to any component(s) of the IMP.
24. Current participation in any other interventional clinical trial.
25. Previous randomisation in this clinical trial.
26. 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.
27. Employed at the trial site or directly involved with the planning or conduct of the trial, or immediate family members of such individuals.
28. Legally institutionalised.
29. Pregnant or lactating.

8.4 Screening and screening failures

Subject identification number

Trial participation begins once written informed consent is obtained. Refer to Appendix 3B for details on the informed consent process. Once informed consent is obtained, a subject identification number (subject ID) will be assigned by a central IRT system and the screening evaluations to assess eligibility criteria may begin. 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). This log will include each subject's identity, date of consent and corresponding subject ID so that any subject may be identified if required for any reason. The log must not be copied or retained by LEO. In addition, the investigator will maintain a log of all subjects considered for screening, whether they have provided written informed consent or not (screening log). This log will be anonymous and will include the reason(s) for not entering the trial, if applicable, or the allocated subject ID.

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 screening failure information is required to ensure transparent reporting of screening failure subjects to meet the CONSORT publishing requirements (Schulz et al. 2010) and to respond to queries from

regulatory authorities. Individuals who do not meet the criteria for participation in the trial (screening failures) may not be re-screened. However, if the reason for screening failure is administrative e.g. delayed test results and not due to the subject failing to meet the eligibility criteria, re-screening may be permitted. Individuals who are re-screened will get a new subject ID.

The following data will be collected in the eCRF for screening failures:

- Date of informed consent(s).
- Demographics (date of birth, age, sex, ethnicity, race).
- Reason for screening failure:
    - Failure to meet eligibility criteria (specify which).
    - Withdrawal by subject.
    - Other (specification is required).
- Date of screening failure.
- Any AEs and SAEs.

In case of any SAEs, these must be followed-up as described in Section 13.7.

9 Treatments

9.1 Trial product description

Delgocitinib is a pan-JAK inhibitor, which is presented in this trial as a cream formulation for topical application. Please refer to Panel 4 for further details.

Panel 4: Identification of IMPs

Investigational medicinal product	Formulation	Active ingredient and formulation concentration	Pack size	Source
Delgocitinib cream 1 mg/g	Cream	Delgocitinib cream 1 mg/g	15 g	CCI [redacted]
Delgocitinib cream 3 mg/g	Cream	Delgocitinib cream 3 mg/g	15 g	CCI [redacted]
Delgocitinib cream 8 mg/g	Cream	Delgocitinib cream 8 mg/g	15 g	CCI [redacted]
Delgocitinib cream 20 mg/g	Cream	Delgocitinib cream 20 mg/g	15 g	CCI [redacted]
Delgocitinib cream vehicle	Cream	Vehicle	15 g	CCI [redacted]

9.2 Administration of IMP

The IMP (delgocitinib cream 1, 3, 8, or 20 mg/g or delgocitinib cream vehicle) will be administered as a twice daily topical application for 8 weeks. The applications will be performed approximately 12 hours apart. Instructions for use will be provided.

A thin layer of IMP covering the affected areas will be applied according to the instructions for use. The maximum amount of IMP to be used depends on the size of the affected BSA. One tube of 15 g delgocitinib cream is considered adequate for one application for subjects with BSA of 50%,

The first application of the IMP will occur at the trial site. Prior to the first IMP application, the subject will be instructed how much cream to apply and which area(s) are to be treated. Only the affected area(s) on the skin (excluding scalp) will be treated. If new lesions occur on

initially untreated area(s) of the skin, these new lesions will be treated with IMP as well except if they occur on scalp. Subjects should be advised to contact the investigator before initiating treatment of new lesions.

The IMP application on initially affected areas and new lesions will continue until Week 8 regardless of clearance status.

The last IMP application will occur at the subject's home before the subject attends the visit scheduled at Week 8.

The IMP will be dispensed by the investigational staff at the visits scheduled in Section 4. The IRT will assign the required kit number(s) for each subject at each dispensing visit.

The investigator will use clinical judgement to treat any symptoms connected with an overdose.

9.3 Treatment assignment

Subjects who have been found to meet all the inclusion criteria and not to fulfil any of the exclusion criteria will be randomised centrally at baseline (Day 1) to receive treatment with either delgocitinib cream (1, 3, 8, or 20 mg/g) or delgocitinib cream vehicle. The treatment assignment will occur on the basis of a computer-generated randomisation scheme in a 1:1:1:1:1 ratio.

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

9.3.1 Blinding

The packaging and labelling of the IMPs will contain no evidence of their identity. It will not be possible to differentiate between the IMPs solely by sensory evaluation.

9.3.2 Emergency unblinding of individual subject treatment

While the safety of a subject always comes first, it is still important to carefully consider if unblinding is necessary to ensure a subject's safety. In many cases, IMP discontinuation and knowledge of the possible treatment assignment are sufficient to treat a trial subject who presents with an emergency condition. An emergency unblinding request can be made by the investigators, health care professionals who are not members of the trial staff, or authorised LEO personnel.

Provisions are in place for 24-hour emergency unblinding of individual subject treatment. If emergency unblinding is required, the investigator can unblind a subject's treatment in the IRT. For a requester who is not a member of the trial staff and who does not have access to the IRT (e.g. a physician at an emergency room), a local contact number for the emergency unblinding CRO is provided on the subject card (see Appendix 3B) to be used if the investigator or delegated site staff cannot be reached. The requester will provide the trial ID and subject ID to the emergency unblinding CRO who will immediately reveal the subject's treatment allocation.

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

9.4 Background treatment (emollients)

All subjects must use an emollient twice daily (or more, as needed) for at least 14 days before randomisation; the background treatment should preferably be an additive free, basic bland emollient. After randomisation emollients must not be used concomitantly with IMP on lesional skin. Subjects are however allowed to continue their background emollient treatment on non-lesional skin throughout the trial (including safety follow-up).

9.5 Rescue treatment

If medically necessary (i.e. to control intolerable AD symptoms), rescue medication for AD may be provided to trial subjects at the discretion of the investigator. The investigators should make every attempt to conduct efficacy and safety assessments (for example disease severity scores, safety laboratory assessments) immediately before administering any rescue treatment.

If rescue medication is initiated, the subject must stop treatment with IMP immediately and must not restart treatment with IMP. It must be stated in the eCRF that the subject receives rescue medication.

9.6 Concomitant medication and concurrent procedures

Any medication or vaccine that the subject receives from 6 months prior to baseline (if relevant) through the safety follow-up period must be recorded in the subject's medical record and the eCRF along with details such as:

- Medication name.

- Indication.
- Start and stop date of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose, unit, and frequency.
- Route of administration.
- For topical treatment, the body location must be recorded: it must be recorded if the treatment is within 5 cm (approximately 2 inches) of the treatment area.

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

- Procedure.
- Body location.
- Diagnosis.
- Start and stop date (it will also be recorded if the procedure is ongoing).
- For topical treatments, it must also be recorded if the procedure is inside the treatment area.

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 9.7. Use of emollients is described in Section 9.4.

No concomitant medication is allowed on lesional skin. On non-lesional skin, background treatment, preferably an additive free basic bland emollient, is allowed.

9.7 Prohibited medication and procedures

The medications and procedures listed in Panel 5 are prohibited during the trial. In case any prohibited treatments are used during the trial, they must be recorded as concomitant medication. Any medication prescribed with the intent to treat AD will be regarded as rescue medication. If rescue medication is initiated, the subject must stop treatment with IMP immediately (see Section 9.5).

Panel 5: Prohibited medication and procedures

Medication	Prohibited from	Prohibited to
Systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporine, mycophenolate-mofetil, azathioprine), immunomodulating drugs (e.g. JAK inhibitors), retinoids (e.g. alitretinoin) or corticosteroids (inhaled or intra-nasal steroids corresponding to up to 1 mg prednisone for asthma or rhinitis may be used)	4 weeks prior to baseline	End of trial
Use of tanning beds, phototherapy (e.g. PUVA or UVB therapy) or bleach baths	4 weeks prior to baseline	End of trial
Live attenuated vaccines	4 weeks prior to baseline	End of trial
TCSs, TCIs or topical PDE-4 inhibitors	2 weeks prior to baseline	End of trial
Change in systemic antihistamine therapy	2 weeks prior to baseline	End of trial
Blood products	4 weeks prior to screening	End of trial
Any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, or dupilumab):		
• Any cell-depleting agents including but not limited to rituximab	6 months prior to baseline or until lymphocyte count returns to normal, whichever is longer.	End of trial
• Other biologics	3 months or 5 half-lives, whichever is longer, prior to baseline	End of trial
Any non-marketed drug substance (i.e. an agent which has not yet been made available for clinical use following registration).	4 weeks prior to baseline or 5 half-lives whichever is the longest	End of trial
Topical treatment (e.g. drug, non-drug, wet wraps) on lesional skin other than the use of IMP.	Baseline	End of trial

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

The IMPs will be packaged in individually numbered kits.

Primary and secondary packaging materials will be individually labelled.

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

9.8.2 Storage of trial products

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

The IMP must be stored at 2–8°C (36–46°F) at the trial site. Do not freeze. The temperature during storage should be monitored by a calibrated, stationary, and continuously electronic recording system with alarm and back-up of data. If no alarm is triggered, a log must be printed, reviewed, signed and dated each month. If the alarm is triggered, the log must be immediately printed, reviewed, signed and dated, and appropriate follow up action will be taken in accordance with the trial product handling manual.

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

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

In the situations listed below, site staff should not use the affected IMPs 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 IMP should be documented in the IRT and reported as a product complaint to Global Pharmacovigilance, LEO (see Section 9.10). Damaged IMP may not be used.

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

9.8.3 Drug accountability

IMP 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.

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

The subjects will return used, and unused IMP (including packaging material) at the visits specified in the schedule of trial procedures (Section 4).

Returned trial products (used, and unused IMP [including packaging material]) can be stored at room temperature and must be stored separately from non-allocated trial products.

All IMPs (including packing material) supplied by the CMO on behalf of LEO will be returned to the CMO on an ongoing basis. Prior to return, the IMP must be fully accounted for by the CRA with the help of site staff responsible for dispensing the IMPs.

All tubes returned to the CMO will be weighed to determine the amount of IMP used.

Reporting in eCRF
The kit/tube number, date of IMP dispensation and return, and number of tubes dispensed and returned will be recorded in the eCRF.

9.8.4 Treatment compliance

The first application of IMP will occur at the trial site with clear instructions from the site staff on which areas of the skin the IMP must be applied and what amount of IMP to be used per application.

At the phone call scheduled on Day 4 and at each visit scheduled in the treatment period (see Section 4), the subject will be asked if they have used the IMP as prescribed. If a subject is found to be non-compliant, the investigator must remind the subject of the importance of following the instructions given, including applying the IMP as prescribed. Compliance or non-compliance, i.e. number of missed IMP applications and the reason for it, must be recorded in the eCRF.

9.8.5 Trial product destruction

Used and unused IMPs will be destroyed by the CMO according to approved procedures and/or local requirements.

9.9 Provision for subject care following trial completion

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

9.10 Reporting product complaints

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

Critical complaints (defined as any defect or issue that has or potentially could have a serious impact for the subject (e.g. SAE) must be reported to Global Pharmacovigilance, LEO within 24 hours.

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

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

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

Global Pharmacovigilance, LEO contact information for reporting product complaints:

Fax number: CCI [redacted]

E-mail address: CCI [redacted]

10 Discontinuation and withdrawal

10.1 General principles

A subject may withdraw from the trial (i.e. withdraw from treatment and protocol-defined interventions) or permanently discontinue trial treatment (i.e. stop treatment only but agree to continued protocol-defined interventions) at any time (prior to first dose or during the treatment period) if the subject, the investigator, or LEO considers that it is not in the subject's best interest to continue.

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the subject's source documentation.

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

Data to be recorded in the eCRF
The primary reason for withdrawal from the trial and discontinuation of IMP must be recorded in the medical records and on the end of trial form in the eCRF where the following options are available:

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

If 'adverse event' or 'other' is selected, a specification must be provided in the eCRF with a clear link to the specific AE if applicable.

10.2 IMP discontinuation rules

10.2.1 Reasons for discontinuation of IMP

Subjects will discontinue IMP in the event of:

- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.
- Evidence of pregnancy.
- Initiation of rescue medication.
- Clinically important laboratory abnormalities:
    - Alanine aminotransferase and/or aspartate aminotransferase values >3×ULN with total bilirubin >2×ULN (unless elevated bilirubin is related to Gilbert-Meulengracht Syndrome).

- Confirmed aspartate aminotransferase and/or alanine aminotransferase >5×ULN (for more than 2 weeks).

- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status.
- Lymphopenia (lymphocytes <0.5x10^9/l; grade 3 according to CTCAE v5.0) confirmed by repeated measurement within 7 days.

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

10.3 Early termination assessments

An end of trial form must be completed for all subjects, including subjects who withdraw from the trial or discontinue IMP treatment, at their last trial visit (the early termination visit, the safety follow-up visit, or the primary endpoint visit, whichever comes last).

Withdrawal from trial
Subjects who withdraw from the trial must 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.

Discontinuation of IMP
Subjects who discontinue IMP for any reason prior to Week 8 will be asked to attend an early termination visit as soon as possible after last application of IMP and return to the trial site for 2 additional visits as indicated below. See the schedule of trial procedures (Section 4) for data to be collected at these visits.

Subjects who discontinue IMP prior to Week 8 will be asked to attend:

- Early termination visit (as soon as possible after the last IMP application).
- Safety follow-up visit (2 weeks after last application of IMP).
- Primary endpoint visit (8 weeks after the first IMP application).

10.4 Lost to follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails 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 to retrieve eDiary and unused IMP and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject. Should the subject continue to be unreachable, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

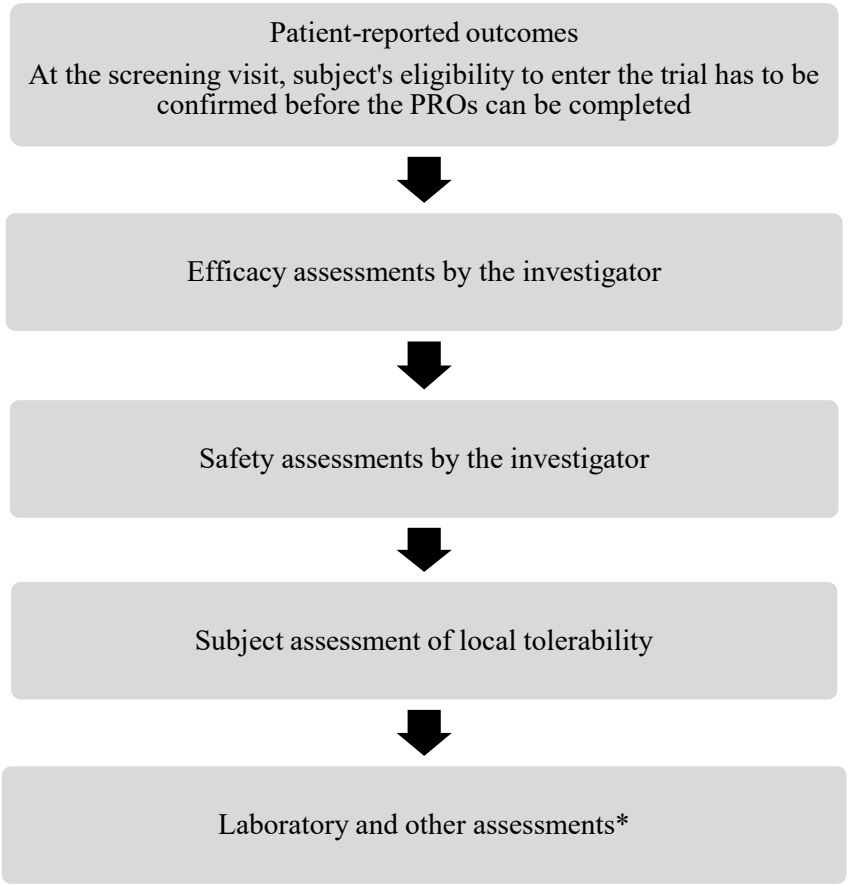
11 Trial assessments and procedures

11.1 Overview

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

Assessments and procedures at each trial visit should be performed in the following order as shown in Panel 6:

Panel 6: Sequence of assessments



* Blood sampling for PK, skin swabs, skin biopsies (optional) and photography of biopsied areas (recommended).

Subjects participating in the trial will be under careful supervision of a principal investigator who must be a dermatologist or allergist. Investigators must be experienced in treating AD and have documented experience and/or training in use of the assessments required by the

protocol and must be either a physician, certified physician's assistant, or advanced registered nurse practitioner.

Whenever possible, the same investigator should perform all the evaluations for a given subject throughout the entire trial period to reduce inter-rater variability.

AEs must be assessed by medically qualified personnel (i.e. adequately trained medical doctors) (Section 13.2).

11.2 Assessments performed only at screening/baseline

11.2.1 Demographics

The following demographic data will be recorded:

- Date of birth. If full date of birth is not allowed to be recorded, month and year of birth should be collected together with the subject's age.
- Sex: female, male.
- Race: American Indian or Alaska native, Asian, black or African American, native Hawaiian or other Pacific islander, white, other (requires a specification to be provided).
- Ethnic origin (self-reported by the subjects): Hispanic or Latino, not Hispanic or Latino.

11.2.2 Fitzpatrick skin type

The subject's skin type will be recorded using the Fitzpatrick skin classification (Panel 7).

Panel 7: Fitzpatrick skin classification

Skin type	Description
I	Individuals who never tan and always sunburn if exposed to any appreciable amount of sunlight, primarily red-headed individuals and lightly complected blondes.
II	Individuals who frequently burn but are able to tan to a small degree after extended sun exposure.
III	Individuals who burn infrequently and tan readily.
IV	Individuals who rarely burn and tan heavily with moderate sun exposures, especially individuals of Asian, American Indian, Mediterranean and Latin American descent.
V	Individuals who have dark constitutive pigmentation but become noticeably darker with sun exposure, especially light complected black individuals, those of Indian descent.
VI	Individuals who have the heaviest constitutive pigmentation, especially dark skinned black individuals.

11.2.3 Medical history

Relevant medical history from the subject's birth must be recorded.

- Skin disease history: all past and current skin disease history including:
    - Alopecia.
    - Vitiligo.
    - Herpes simplex.
- Atopy history:
    - Onset of AD disease.
    - Previous treatments for AD.
    - Asthma.
    - Food allergy.
    - Hay fever.

- Allergic conjunctivitis.
- Atopic keratoconjunctivitis.
- Cataract.
- Glaucoma.
- Eczema herpeticum.

- 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 or whether it is ongoing will be recorded.

11.2.4 Height and weight

The subject's height (without shoes) will be measured; the subject's weight (in indoor clothing and without shoes) will be measured.

11.2.5 Body surface area involvement

The total BSA affected by AD will be assessed by the investigator for each section of the body component A of SCORAD (see Section 11.3.3) and will be reported as a percentage of all major body sections combined. The following body regions will be assessed (with the highest possible score for each region in brackets): head and neck (9%), anterior trunk (18%), back (18%), upper limbs (18%), lower limbs (36%) and genitals (1%).

The total BSA score will be assessed according to the schedule of procedures (Panel 2).

11.3 Efficacy assessments

11.3.1 Eczema Area and Severity Index (EASI)

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (Hanifin et al. 2001, Tofte et al. 1998). 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 EASI score will be calculated automatically.

Panel 8: Calculation of the Eczema Area and Severity Index

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

AS, area score; EASI, Eczema Area and Severity Index; SS, severity score. Modified from (HOME website).

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

EASI, Eczema Area and Severity Index

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

The vIGA-AD is an instrument used in clinical trials to assess the subject's global disease severity and is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Panel 10). The vIGA-AD score will be assessed at time points 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. New lesions that occurred on previously untreated areas will be included in the assessment.

The vIGA-AD score is selected using the descriptors in Panel 10 that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under morphological description be present.

Panel 10: 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.

Reference: Eli Lilly and Company 2017

11.3.3 Scoring Atopic Dermatitis (SCORAD)

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

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

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

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

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

0 = None/absent

1 = Mild

2 = Moderate

3 = Severe

Note: dryness is evaluated on uninvolved areas.

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

Subjective symptoms (C)
A subjective assessment of the average itch and sleeplessness over the last 3 days/nights is recorded for each symptom by the subject on a visual analogue scale, where 0 is no itching (or no trouble sleeping) and 10 is unbearable itching (a lot of trouble sleeping), with a maximum possible score of 20. The subjective assessment will be completed by the subjects together with the PROs using the electronic device.

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

11.4 Safety assessments

11.4.1 Vital signs

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

If an abnormal vital sign at screening is considered to be clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be randomised into the trial (respecting exclusion criterion no. 20).

In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later with subjects resting in a supine position 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. If the third measurement confirms the first measurement (abnormal), the second measurement will be considered false. Only the last value measured and considered correct will be recorded in the eCRF.

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

11.4.2 Physical examination

A thorough physical examination of the subject including whole body inspection of the skin and auscultation of heart, lungs and abdomen; palpitation of the abdominal organs and basic neurological status must be performed according to the schedule of trial procedures (Section 4). The investigator should perform the same examinations as in clinical practice as a minimum.

If the screening physical examination results in a finding, which 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 (respecting exclusion criterion no. 20).

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

Clinically significant abnormal 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 will be reported as an AE in accordance with Section 13.3.

11.4.3 ECG

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

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

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

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

If the screening ECG results in a finding, which 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 (respecting exclusion criterion no. 20).

The collection and transmission of ECG data will be described in a separate ECG manual. Test dummy transmissions will be undertaken prior to the trial conduct to ensure that transmissions can be made, and that date and time settings are correctly set.

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

Clinically significant abnormal 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 will be reported as an AE in accordance with Section 13.3.

11.4.4 Laboratory testing

Blood and urine samples will be collected according to the schedule of trial procedures (Section 4). See Panel 11 for an overview of the individual clinical laboratory parameters to be assessed in this trial.

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

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 (respecting exclusion criteria no. 16, 20, 21, 22, and 29).

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

Tests performed at the trial site
Urine samples will be tested at the trial site with a dipstick; if abnormal, a urine sample will be sent to the central laboratory for further analysis.

Women of childbearing potential will have a urine pregnancy test performed at the trial site at visits indicated in the schedule of trial procedures in Section 4.

Panel 11: Clinical laboratory tests

Chemistry	Haematology
Sodium Potassium Creatinine Urea nitrogen Calcium Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Gamma glutamyl transferase Bilirubin[a] Lactate dehydrogenase Cholesterol LDL cholesterol HDL cholesterol Triglycerides Glucose (non-fasting) Albumin Protein C-reactive protein	Erythrocytes Haematocrit Haemoglobin Erythrocyte mean corpuscular volume Erythrocyte mean corpuscular haemoglobin concentration Leukocytes Neutrophils, neutrophils/total cells Lymphocytes, lymphocytes/total cells Monocytes, monocytes/total cells Eosinophils, eosinophils/total cells Basophils, basophils/total cells Thrombocytes
	Serology[b]
	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 Immunoglobulin E
	Tuberculosis test[b,c]
	Interferon gamma release test
Urinalysis[d]	**Serum pregnancy test[b,e]**
Protein Glucose Ketones Occult blood Leukocytes Nitrite	Choriogonadotropin beta

a) If bilirubin is above ULN, direct and indirect bilirubin will also be measured.
b) Measured at screening only
c) Subjects with high risk of latent tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested.
d) Urine samples will be tested at the trial site (dipstick). In case of abnormal dipstick results, a urine sample will be sent to the central laboratory for microscopic examination (leukocytes, erythrocytes, and casts)
e) Only female subjects of childbearing potential. In addition, urine pregnancy tests will be performed at the trial site.

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

Reporting in eCRF

The site staff will record in the eCRF if a sample was taken and the investigator's assessment of the results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant').

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 as well as any new clinically significant sign, symptom or illness will be reported as an AE in accordance with Section 13.3.

11.4.5 Subject assessment of local tolerability

Subjects will provide an assessment of local tolerability according to the schedule of trial procedures (Section 4).

The subject will retrospectively be asked by the investigator to assess stinging/burning in connection with the IMP applications since their last visit. The highest (worst) skin reaction score across treatment area(s) will be recorded in the eCRF by use of the 4-point scale shown in Panel 12.

Panel 12: Subject assessment of local tolerability after IMP application

Grade	Stinging/burning
0 (none)	No stinging or burning
1 (mild)	Slight warm, tingling sensation, not really bothersome
2 (moderate)	Definitive warm, tingling sensation, that is somewhat bothersome
3 (severe)	Hot, tingling/stinging sensation that has caused definite discomfort

Subject assessment of local tolerability will be performed after safety assessments by the investigator (Panel 6). Local tolerability reactions are not reported as AEs; however, if they qualify as an SAE, they will be reported as described in Section 13.4.1.

11.5 Pharmacokinetic assessments

11.5.1 Blood sampling for analysis of systemic concentration of delgocitinib

A single blood sample for PK assessment will be collected for each subject after 2–6 hours after the morning application of IMP as specified in the schedule of trial procedures (Section 4). The PK blood sample should be collected from a non-treated area.

It will be recorded in the eCRF if the PK blood sample was taken; if not, a reason will be provided. The date and time of the last IMP application prior to the PK sample being taken must be recorded in the eCRF.

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

Plasma samples for determination of delgocitinib concentration will be analysed by a laboratory using a validated bioanalytical method. Details of the analytical method used will be described in the bioanalytical report.

Samples from delgocitinib cream vehicle-treated subjects will not be analysed. Written procedures are in place to avoid unblinding of the trial and any trial subjects in relation to analysis of the PK samples.

11.6 Pharmacodynamics and pharmacogenomics

11.6.1 Overview

Normal skin is colonised by a wide variety of microorganisms, including fungi, viruses, and bacteria. The skin microbiome is complex and diverse and varies between individuals and anatomical sites (Costello et al. 2009). It has been known for years that some skin diseases are associated with dysbiosis of the skinbiome. AD has long been associated with increased skin colonisation with *S. aureus*. Indeed, *S. aureus* colonisation has been proposed to play an important role in AD pathophysiology via bacterial production of specific virulence factors (Cardona et al. 2006). Increased colonisation with *S. aureus* in AD is accompanied by decreased colonisation with many commensal bacterial species, resulting in overall decrease in bacterial diversity (Kong et al. 2012). Resolution of active-disease in AD in response to therapy correlates with reduction of *S. aureus* colonisation and increase in microbiome diversity (Kong et al. 2012).

The present trial will use sequencing to identify specific strains of bacteria present on the skin and thus characterise treatment effects on the skin microbiome in AD subjects.

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

11.6.2 Skin swabs

A total of 4 skin swabs for microbiome and *S. aureus* measurements will be taken at the time points specified in the schedule of trial procedures (Section 4).

At baseline (Day 1), 2 skin swabs are to be taken:

- 1 skin swab from a representative lesional area. The location should be selected so that a similar non-lesional body location can be identified.
- 1 skin swab from a non-lesional area at an anatomically similar site to the lesional skin swab.

At Week 8 (end of treatment), 2 skin swabs will be taken at the same locations as the baseline skin swabs.

If biopsies are to be taken (see Section 11.6.3), the baseline biopsies will be taken from the same area as the skin swabs, so the sites selected for skin swabs must then also be appropriate for biopsying.

It will be recorded in the eCRF if the skin swabs were taken and from which location (volar arm, lower limbs, trunk, other); if skin swabs were not taken, a comment will be provided.

Subjects will be instructed not to shower or wash their body for at least 10 hours prior to the baseline visit and Week 8 visit.

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

11.6.3 Skin biopsies and photographs (all sites, but optional)

Subjects who have lesions at a location suitable for biopsying (i.e. volar arm, lower limbs, trunk, other) will be asked to participate in an exploratory component involving skin biopsies. Participation in this component of the trial requires that the subject provides additional informed consent and is not mandatory for participation in the trial. Biopsies will not be taken if the investigator considers the procedure unsuitable for the subject (e.g. subjects receiving anticoagulant therapy).

It is expected that approximately half of the eligible subjects will accept to participate in this exploratory component of the trial. If biopsies are obtained from less than 10% of subjects, analysis may not be carried out as the number of biopsies may be to too low to allow for a meaningful analysis. A final decision will be made after unblinding.

The skin biopsies will be used to analyse the expression of genes involved in the pathogenesis of AD including inflammatory genes, genes involved in immune function and genes involved in skin differentiation and barrier function. If deemed relevant transcriptome profiling of some or all of the biopsies may be done. The purpose is to assess if changes in gene expression precedes the clinical effect of JAK inhibition and to show disease resolution also at the molecular level.

A total of four skin biopsies (2 mm) will be taken at the timepoints specified in the schedule of trial procedures (Section 4): at baseline (lesional and non-lesional skin), after 1 week of treatment (lesional only) and at end of treatment (lesional only).

Skin biopsies will be taken from the same body location as the skin swabs. It will be recorded in the eCRF if the biopsy was taken and from which body location (volar arm, lower limbs, trunk, other); if not, a comment should be provided. All four biopsies will be from an anatomically similar body location to the extent possible.

A check of skin biopsy wound healing including removal of suture, if applicable, will be performed at the next trial visit as specified in the schedule of trial procedures (Section 4).

The biopsies will be transferred to RNAlater (RNA stabilisation) solution immediately after being collected and placed at 2–8°C for 16–30 hours. The sample will then be transferred to a clean tube and stored at <-20°C in suitable rack and kept until shipment to the central laboratory for further processing. Further instructions for collection, handling, and shipment for skin biopsy samples are provided in a laboratory manual.

It is recommended to document the biopsied areas with photographs taken before biopsying and immediately after, both at baseline, after 1 week of treatment and at the end of treatment, using digital photography assessments. This will serve both as a documentation of the biopsy site and to show disease progression over time. The photography component for the skin biopsies is recommended and not mandatory.

The trial sites participating in this photography component will be expected to use their own equipment to take the photographs. Instructions and specifications for photography will be provided in a photography manual.

The photographs will have no other subject identifier than the subject ID and visit number and will be transmitted electronically using a secure file transfer protocol. Features that could potentially be used to identify the subject e.g. tattoos or jewelry will be removed from the photographs before they are transferred to LEO.

Printed copies of the photographs must be included as part of the individual subject source documentation.

LEO may at its discretion use the photographs in publications, posters, and similar types of information material or media targeting patients and health care professionals. The photographs may also be part of training material used for training and educational purposes. Steps will be taken to ensure that the identity of the subject is protected to the extent possible.

11.7 Other assessments

11.7.1 Patient-reported outcomes (PROs)

Each subject must make individual assessments relating to their perception of their disease and quality of life. These will be performed prior to the investigator performing his/her efficacy assessments. At the screening visit, the subject's eligibility needs to be established before the PROs can be completed.

The subjects will receive an eDiary device and eDiary training, as well as complete all of the PROs (except TSQM), at the screening visit. Completion of the eDiary will be initiated at the latest 1 week prior to the baseline visit (Day 1).

Two PROs will be assessed daily using an eDiary:

- ADSD.
- Eczema-related Sleep NRS.

The subjects must complete the eDiary each day in the evening, and compliance with the eDiary completion will be reviewed by the trial site staff throughout the trial. The eDiary should be returned to the trial site as outlined in the schedule of trial procedures (Section 4).

In addition, 8 PROs will be completed on an electronic device by the subjects at the trial sites at the visits specified in the schedule of trial procedures (Section 4). The PROs will be completed in the following order:

- POEM.

- DLQI.
- PGI-S.
- PGI-C.
- SF-36.
- EQ-5D-5L.
- WLQ.
- TSQM.

11.7.1.1 Atopic Dermatitis Symptom Diary (ADSD)

ADSD is a symptom diary developed by LEO. CCI [redacted]

11.7.1.2 Eczema-related Sleep Numeric Rating Scale (Eczema-related Sleep NRS)

Eczema-related Sleep NRS is a scale developed by LEO. Subjects will rate how much their eczema interfered with their sleep the previous night using an 11-point NRS (0 indicating it 'did not interfere' and 10 indicating that it 'completely interfered'). Subjects will complete the Eczema-related Sleep NRS as part of an eDiary each day in the evening at the latest from Week -1 to Week 8.

11.7.1.3 Patient-Oriented Eczema Measure (POEM)

POEM is a validated questionnaire used to assess disease symptoms in AD patients in both clinical practice and clinical trials (Charman et al. 2004).

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

indicative of a worse disease severity. The POEM will be completed at the trial site according to the schedule of trial procedures (Panel 2).

11.7.1.4 Dermatology Life Quality Index (DLQI)

DLQI is a validated questionnaire with content specific to those with dermatology conditions. It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their quality of life over the last week. These include dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships and the treatment (Finlay & Khan 1994). Each item is scored on a 4-point Likert scale (0='not at all/not relevant'; 1='a little'; 2='a lot'; 3='very much"). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor quality of life. The DLQI will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.1.5 Patient Global Impression of Severity (PGI-S)

PGI-S is a single item designed to capture the subject's overall perception of their eczema over the past week on a 4-point categorical response scale ('none' to 'severe'). The PGI-S will be completed at the trial site according to the schedule of trial procedures (Section 4).

11.7.1.6 Patient Global Impression of Change (PGI-C)

The PGI-C is a 1-item questionnaire designed to assess the subject's overall impression of changes (FDA public workshop on Guidance 3 2018). The subjects have to select the one response from the response options ('much better', 'a little better', 'no change', 'a little worse', or 'much worse') that best describes the overall change in their eczema since they started IMP treatment. The PGI-C will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.1.7 36-item Short Form Health Survey (SF-36)

The SF-36v2 (Acute Recall) is a 36-item scale constructed to survey health status and quality of life (Ware & Sherbourne 1992). The acute recall version asks subjects to reply to questions according to how they have felt over the previous week. Subjects will be asked to answer each item by selecting one of 3 to 6 categorical response options.

The SF-36v2 (Acute Recall) yields scores for 8 health domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) and 2 psychometrically derived summary scores (a physical component summary and a mental component summary).

The SF-36 will be completed according to the schedule of trial procedures in Section 4.

11.7.1.8 EuroQol 5-dimension health questionnaire 5-level (EQ-5D-5L)

EQ-5D-5L is a standardised measure of health status developed by the EuroQoL group to provide a simple, generic measure of health for clinical and economic appraisal (Greiner et al. 2003). The EQ-5D-5L is a self-administered questionnaire used to assess health status 'today' and is divided into 2 sections. The first section includes 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression); each dimension will be assessed by the subject using a 5-point Likert scale ('no problems', 'slight problems', 'moderate problems', 'severe problems', and 'extreme problems'). The second section consists of a vertical visual analogue scale anchored at 0 ('the worst health you can imagine') and 100 ('the best health you can imagine'). The EQ-5D-5L will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.1.9 Work Limitation Questionnaire (WLQ)

WLQ is a validated questionnaire to measure the degree to which health problems interfere with specific aspects of job performance and the productivity impact of these work limitations (Lerner et al. 2001). It asks subjects to rate their level of difficulty or ability to perform 25 specific job demands in the last 2 weeks. Responses to the 25 items are combined into 4 work limitation scales: time management, physical demands, mental/interpersonal, and output demands. These capture the multidimensionality of job roles and also reflect an important characteristic of many chronic illnesses, in that they may result in limitations in performing some activities but not others. Scale score range from 0 ('limited none of the time') to 100 ('limited all the time'). The WLQ will be completed at the trial site for subjects with a paid job according to the schedule of trial procedures in Section 4.

11.7.1.10 Treatment Satisfaction Questionnaire for Medicine (TSQM)

The TSQM v. II is a generic questionnaire assessing subject's satisfaction with the treatment (Atkinson et al. 2004). The tool consists of 11 items addressing four domains (effectiveness, side effects, convenience and overall satisfaction). Ten items will be assessed by the subject using a 7-point scale ('extremely dissatisfied', 'very dissatisfied', 'dissatisfied', 'somewhat satisfied', 'satisfied', 'very satisfied', and 'extremely satisfied'). However, one item will be assessed using a 2-point scale ('yes' and 'no'). The score ranges from 0 to 100 with higher scores indicating higher satisfaction. The TSQM will be completed at the trial site according to the schedule of trial procedures (Panel 2).

11.7.2 Atopic dermatitis lesions on scalp

Subjects with AD lesions on scalp are not allowed to enter the trial and if AD lesions occur on the scalp during the trial these should not be treated with IMP.

Whether subjects have AD lesions on scalp will be captured in the eCRF as specified in the schedule of trial procedures (Section 4).

11.8 Estimate of total blood volume collected

Blood samples will be drawn for haematology, biochemistry, serology, PK, and serum pregnancy test (females of childbearing potential only). The total volume of blood to be drawn is approximately 39 mL.

11.9 End of trial

An end of trial form must be completed in the eCRF for all randomised subjects (including subjects who permanently discontinue IMP and subjects who withdraw from trial). The following data will be collected:

- Whether the subjects completed the trial.
- Last trial site visit or contact number for which data is recorded.
- Date and time of last application of IMP.
- Primary reasons for discontinuation from IMP, withdrawal from trial, and not attending primary endpoint visit, if applicable (lack of efficacy, AE, withdrawal by subject, lost to follow-up, pregnancy, death, other).

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

11.10 Storage of biological samples

PK samples and skin biopsies will be retained for as long as the quality of the material permits evaluation but for no longer than 12 months after completion of the CTR unless specific additional consent has been obtained that allows storage for future research (see below).

Biobank

This protocol includes the collection and analysis of different biological samples. If consent is given by the subject, LEO will store skin biopsies and skin swabs collected in a biobank established by LEO and hosted by BioStorage Technologies GmbH. The residual biological samples will be used for future research performed by LEO. Donation of the samples for future research is voluntary and subjects must give their separate written consent to confirm donation and storage and the terms associated herewith. The samples will be transferred from the relevant laboratory to the biobank. The samples will be labelled with the trial ID, subject ID, and the sample date to protect the privacy of the subjects and to allow continued blinding for future analyses. The samples from this trial will be stored in the biobank for up to 10 years after the end of the trial and will then be destroyed.

12 Scientific rationale for trial design and appropriateness of assessments

This is a multi-centre, randomised, vehicle-controlled, double-blind, parallel-group trial, which will be conducted in accordance with the protocol, ICH-GCP and applicable regulatory requirements.

The trial will be conducted at multiple trial sites located in North America (USA and Canada) and Australia. High-quality trial sites with shared standards of practice and values will be selected.

Patients with AD represent a heterogeneous patient population with disease severity ranging from mild to severe. To mitigate any potential difference in trial outcome based on baseline characteristics, eligibility criteria for inclusion have been carefully selected and trial subjects will be randomised in stratified manner as described in Section 9.3. The randomisation will minimise selection bias and minimise influence of (intrinsic) confounding factors and the stratification will ensure a certain balance of the treatment groups with respect to disease severity and region.

The most important inclusion criteria for entry into the trial is a diagnosis of AD (as defined by the Hanifin and Rajka 1980 criteria (Hanifin & Rajka 1980, Appendix 6) and history of AD for at least 1 year, to ensure correct diagnosis and rule out differential diagnosis.

The inclusion of 4 active treatment arms with 1, 3, 8 and 20 mg/g of delgocitinib cream and a vehicle control group is considered enough to establish a dose-response signal. The vehicle control group will serve as reference and has been added to establish the efficacy and safety of the delgocitinib cream in a blinded trial design.

The trial endpoints have been selected to evaluate the efficacy of delgocitinib in improving the severity and extent of AD. EASI, vIGA-AD and SCORAD will be used in this clinical trial as investigator-rated assessments of disease severity. EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (Hanifin et al. 2001, Tofte et al. 1998). vIGA-AD is a validated instrument used in clinical trials to assess the subject's global AD and SCORAD is a validated tool to assess the extent and severity of AD lesions and subjective symptoms (European Task Force on Atopic Dermatitis 1993). The primary endpoint of the trial is to evaluate the change in EASI score from baseline to Week 8. The trial endpoints will also address subject's perception of disease severity and the impact on sleep, daily activity, and health-related quality of life, and safety.

The duration of this trial is 8 weeks. This duration - based on results from a phase 2a trial in adults with the ointment formulation (Nakagawa et al. 2018) - is considered to be sufficient to evaluate the duration required for optimal treatment effect.

13 Adverse events

13.1 Definition and classification of adverse events

AEs and SAEs are defined in Appendix 1.

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

13.2 Collection of adverse event reports

AEs must be collected from time of first trial-related activity after the subject has signed the ICF until completion of the clinical trial for the individual subject (defined as safety follow-up visit 2 weeks after the last IMP administration).

AEs must be assessed by medically qualified personnel.

At all visits, the subject will be asked a non-leading question by the investigator about AEs, for example: “How have you felt since I saw you last?” No specific symptoms should be asked for. It is important that the investigator also observes the subject for any changes not reported by the subject and records these changes. If a subject report an AE during the phone call on Day 4, it is up to the investigator’s discretion to perform an unscheduled visit.

Refer to Sections 11.4.1 to 11.4.4 for principles for data entry in the eCRF.

13.3 Reporting of adverse events

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

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

For cutaneous AEs, the *location* must be part of the AE description and may be described as [e.g. the face, scalp, back, chest, arm, leg, trunk or limb]. Additionally, the location should be described using the following terminology:

- Lesional/perilesional (≤2 cm from the border of lesion(s) treated with IMP).
- Distant (>2 cm from the lesion border).

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

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

Action taken with IMP: any action taken with IMP as a consequence of the AE must be recorded (dose not changed, 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).

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

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

Global Pharmacovigilance at LEO

E-mail address: CCI [redacted]

Fax number: CCI [redacted]

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

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

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

13.4.2 LEO reporting responsibilities

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

For the IMP, the Investigator's Brochure for delgocitinib cream, edition 1 and subsequent updates must be used.

Global Pharmacovigilance at LEO 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** (ICH E2A Guideline), and which are unexpected (SUSARs), are subject to expedited reporting to regulatory authorities and IEC(s)/IRB(s) according to the current applicable legislation in the concerned country. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

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

13.5 Other events that require expedited reporting

13.5.1 Pregnancy

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

The completed Pregnancy Forms must be faxed or scanned and e-mailed to Global Pharmacovigilance at LEO. 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 Adverse events of special interest

The event listed in Panel 13 is considered an AESI in this trial and will require that the investigator provides additional details to be recorded in the eCRF. An AESI may be serious (requiring expedited reporting, Section 13.4) or non-serious.

Panel 13: Adverse events of special interest

Adverse event of special interest	Additional information to be provided
Eczema herpeticum	Skin findings: • Lesion type. • Disseminated/localized. • Location. • Present in area with visible eczema/no visible eczema/present in areas with and without eczema. • Monomorphic/polymorphic. Confirmation of herpes simplex virus.

13.6.2 Overdose

An overdose is defined as a subject using more than the recommended quantity of IMP specified in this protocol in Section 9.2 (at the investigator's discretion). An overdose is either accidental or intentional.

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

13.6.3 Medication error

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

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

13.6.4 Misuse

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

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

13.6.5 Abuse

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

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

13.6.6 Aggravation of condition

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

13.7 Follow-up for final outcome of adverse events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). Once a subject leaves the clinical trial, the investigator should follow up on the outcome of all non-serious AEs classified as of possibly/probably relationship to the IMP for 14 days or until the final outcome is determined, whichever comes first. SAEs must be followed up until a final outcome has been established, that is, the follow-up may continue beyond the end of the clinical trial. For SAEs which have stabilised and cannot be expected to recover during the trial or the safety follow-up periods, for example chronic or stabilised conditions, 'not recovered' is accepted as a final outcome and a statement that the SAE has stabilised or is chronic should be added to the narrative in 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.*" (EU Directive 2001/20/EC).

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

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

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

14 Statistical methods

14.1 Sample size

A total of 250 subjects will be randomised 1:1:1:1:1 to one for the following 5 treatment groups: delgocitinib cream 1 mg/g, 3 mg/g, 8 mg/g, 20 mg/g or delgocitinib cream vehicle.

The sample size is based on the following pairwise consideration, even though the primary objective of the trial is to establish the dose-response relationship: With a significance level of 5% when comparing two treatment groups and assuming a difference in the mean change from baseline to Week 8 in EASI of 7 (with a standard deviation of 9 for each treatment group) between an investigational dose (delgocitinib cream) and delgocitinib vehicle, then 50 subjects per treatment group will provide a nominal power of at least 95% to detect a difference between two treatment groups. With 35–40 subjects per treatment group (e.g. in the subgroups of subjects with moderate or severe AD), there is approximately 90% power to detect a difference of 7 in mean change from baseline to Week 8 in EASI.

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All randomised subjects exposed to IMP will be included in the full analysis set and will be analysed for efficacy parameters up to Week 8. Exclusions from the full analysis set can be considered in special cases as described in ICH E9, Section 5.2.1, Full Analysis Set. If it is decided to exclude a subject from the full analysis set, a justification addressing ICH E9 will be given.

A per protocol analysis set will be defined by excluding subjects from the full analysis set who fulfil any of the following criteria:

- Did not provide EASI or vIGA-AD data following start of treatment.
- Are known to have taken the wrong IMP throughout the treatment period of the trial.
- Did not fulfil the disease defining inclusion criteria (that is, inclusion criteria 3, 4, 5, and 6).
- Did not apply IMP at least 80% of the time in the period from date of first application of IMP to date of last application of IMP.

A safety analysis set will be defined as all randomised subjects exposed to IMP.

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

14.3 Statistical analysis

14.3.1 Disposition of subjects

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

14.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects by treatment group. Presentations of demographics, baseline disease severity, and proportion of subjects with baseline worst pruritus ("itch" – one of the symptoms captured in ADSD) (weekly average) above/below 4 on the NRS scale will also be given by region (North America (US and Canada) and Australia) and baseline disease severity (baseline vIGA-AD of 2, 3, and 4).

Demographics include age, sex, race, and ethnicity. Other baseline characteristics include vital signs, height, weight, body mass index, total IgE, Fitzpatrick skin classification, 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

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

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

Drug accountability data will be calculated by subtracting the weight of the used tubes from the mean normal weight of full tubes. Average weekly/bi-weekly and total usage will be presented per treatment group, respectively, both for time intervals between visits (1 or 2-week periods depending on the time between site visits) and total period.

Adherence to treatment regimen will be recorded in the eCRF. If any complications or deviations in administration are observed, these will be described as protocol deviations.

Adherence will be presented for the safety analysis set for each treatment group via the percentage of applications missed.

14.3.4 Testing strategy

This is a dose-ranging trial with the primary objective to establish the dose-response relationship. For the primary endpoint, change from baseline to Week 8 in EASI score, and the secondary endpoints, EASI75 at Week 8 and vIGA-AD TS, the selection of the dose-response model that fits data best will be controlled using a family-wise error rate of 5%. There will be no adjustment for the multiple testing of primary and secondary endpoints, all p-values will be considered nominal.

14.3.5 Analysis of primary efficacy endpoint

The primary endpoint, change from baseline to Week 8 in EASI, will be analysed for the full analysis set and for the per protocol analysis set. The per protocol analysis is regarded as supportive.

For the analysis of the change from baseline to Week 8 in EASI, data collected after permanent discontinuation of IMP or after initiation of rescue medication will not be included in the analysis. Missing data at Week 8 will be imputed using the MMRM predicted values from the below specified model for repeated measurements.

The MCP-Mod approach (see e.g. EMA Qualification Opinion of MCP-Mod or Bretz et al. 2005 for further details of the framework) will be used to guide dose selection. The dose-response relationship for the continuous endpoint Change from baseline to Week 8 in EASI will be modelled by the following 3 identified candidate models. These candidate models are selected based on the expected dose-response.

Linear in log: $E_0 + \delta \times \log(d + c)$,

Emax: $E_0 + E_{max} \times d / (ED_{50} + d)$,

Sigmoid Emax: $E_0 + E_{max} \times d^h / (ED_{50}^h + d^h)$,

where d is the dose (incl. vehicle), E_0 is the efficacy offset (anticipated vehicle effect), E_{max} is the asymptotic maximum effect, ED_{50} is the half-life value of E_{max}, h is the steepness at ED_{50}, δ is the slope parameter, and c is a fixed offset parameter.

The models will be adjusted for the stratification variables region and disease severity (baseline vIGA-AD of 2, 3, and 4). The model parameters (ED_{50}, h) will be prespecified a priori by suitable guesses based on data from Japan Tobacco's dose-ranging trial QBA2-1 (Nakagawa et al. 2018). Akaike's Information Criteria will be used as the goodness-of-fit criterion that will drive the selection of the dose-response model that fits data best while controlling the family-wise error rate at 5%. Based on the selected model, the dose-response relationship will be estimated and presented with 2-sided 95% CI. If none of the candidate models converge, other possibilities of models and goodness-of-fit criteria will be explored. The dose-response modelling will be performed on both the total population and subjects having a baseline vIGA-AD of 3 or 4, in order to further explore heterogeneity in the disease population.

In addition to the dose-response modelling approach, the continuous endpoint will be analysed using an MMRM on the post baseline responses up to Week 8 with an unstructured covariance matrix, Kenward-Roger approximation to estimate denominator degrees of freedom, and the mean modelled as follows:

Change from baseline in EASI

$$= \text{treatment} \times \text{visit} + \text{baseline EASI} \times \text{visit} + \text{region} + \text{baseline vIGA-AD}$$

The estimates will be presented with nominal p-values and 95% CI at each visit. The primary comparison between each delgocitinib dose and vehicle will be at Week 8.

Sensitivity analysis will be performed as applicable in order to assess the robustness of results of the primary analysis with respect to the retrieved data at Week 8 and assumptions regarding missing data. This will be described in further detail in the statistical analysis plan.

14.3.6 Analysis of secondary efficacy endpoints

The secondary endpoints, vIGA-AD TS and EASI75 at Week 8, and time to vIGA-AD TS will be analysed for the full analysis set and for the per protocol analysis set. The per protocol analysis is regarded as supportive.

For the analysis of the secondary binary endpoints, subjects who initiate rescue medication before Week 8 or permanent discontinue IMP and have no retrieved data at Week 8, will all be considered non-responders.

The dose-response modelling approach suggested for the primary endpoint will also be applied for the binary secondary endpoints, vIGA-AD TS and EASI75 at Week 8.

In addition to the dose-response modelling approach, difference in response rates between the delgocitinib doses and vehicle will be analysed separately for each of the dose groups using the Cochran-Mantel-Haenszel test stratified by region and disease severity. The null hypothesis of no difference in response rates between the delgocitinib doses and vehicle will be tested against the 2-sided alternative that there is a difference. Furthermore, a shift table for the vIGA-AD will be presented for baseline to Week 8 per treatment group.

The time to vIGA-AD TS response is defined as the time from baseline to first assessment of a vIGA-AD TS. Subjects will be censored at the date of the last assessment visit or at initiation of rescue medication, whichever occurs first. Kaplan-Meier curves of time to vIGA-AD TS will be estimated and presented by treatment for the full analysis set. Treatment groups will be compared using a 2-sided log-rank test stratified by region and baseline vIGA-AD.

Sensitivity analysis will be performed as applicable in order to assess the robustness of results of the primary analysis with respect to the retrieved data at Week 8, use of rescue medication, and assumptions regarding missing data. This will be described in further detail in the statistical analysis plan.

14.3.7 Analysis of other endpoints

To support the primary and secondary endpoints, EASI50 at Week 8 and EASI90 at Week 8 will be analysed and presented for the full analysis set. Both endpoints will be analysed using the Cochran-Mantel-Haenszel approach as described for the analysis for the secondary binary endpoints.

To support the primary and secondary endpoints on severity and extent of AD, at least 75% reduction in SCORAD score (SCORAD75) at Week 8, SCORAD50 at Week 8, and the change from baseline to Week 8 in SCORAD score will be analysed and presented for the full analysis set. SCORAD50 and SCORAD75 will be analysed using the Cochran-Mantel-Haenszel approach as described for the analysis for the secondary binary endpoints, and the change from baseline to Week 8 will be analysed using the MMRM approach as described for the analysis for the primary endpoint.

14.3.7.1 Analysis of patient-reported outcomes

The PROs POEM, DLQI, PGI-S, PGI-C, SF-36, EQ-5D-5L, WLQ and TSQM will be summarised by treatment group and visit using descriptive statistics. The summaries will be presented for the full analysis set.

The ADSD and Eczema-related Sleep NRS collected in the eDiaries on a daily basis (all individual symptoms) will be summarised over time by treatment group using descriptive statistics. The summaries will be presented for the full analysis set.

The daily diary recordings of the ADSD will be derived into discrete weekly endpoints based on calendar time (with the exception of Week 8) from baseline visit, i.e. the endpoints represent the nominal week and are not directly related to the actual visit in contrast to other visit-based assessments. The algorithm for deriving the endpoints at each time point is described as follows: baseline weekly average will be defined by average of measurements from Day -7 to Day -1, Week 1 weekly average will be defined by the average of measurements from Day 1 to Day 7, Week 2 weekly average will be defined by the average of measurements from Day 8 to Day 14 and so on, until Week 7. Week 8 will be calculated based on the 7 days preceding the Week 8 visit. A minimum of 4 ADSD scores out of the 7 days are required to calculate the average score. This will be derived for each individual symptom, respectively. The same derivation rules will be applied for the Eczema-related Sleep NRS.

In the subgroup of subjects with a baseline worst pruritus (one of the symptoms captured in the ADSD) (weekly average) score of ≥4, the proportion of subjects with reduction in worst pruritus (weekly average) of ≥4 from baseline to Week 8 will be summarised by treatment group and analysed using the Cochran-Mantel-Haenszel approach as described for the analysis of the secondary binary endpoints.

In the subgroup of subjects with a baseline DLQI score of ≥4, the proportion of subjects with a reduction in DLQI score of ≥4 at Week 8 will be summarised by treatment group and analysed as described using the Cochran-Mantel-Haenszel approach for the analysis of the secondary binary endpoints. In addition, the proportion of subjects achieving a DLQI score of 0 or 1 at Week 8 will be presented.

In the subgroup of subjects with a baseline POEM score of ≥4, the proportion of subjects with a reduction in POEM score of ≥4 at Week 8 will be summarised by treatment group and analysed using the Cochran-Mantel-Haenszel approach as described for the analysis of the secondary binary endpoints.

The change from baseline to Week 8 in ADSD (weekly average for each individual symptom), Eczema-related Sleep NRS (weekly average), POEM, DLQI, SF-36, EQ-5D-5L and WLQ will be summarised by treatment group and domain, where applicable, and analysed using the MMRM approach as described for the analysis of the primary endpoint.

The TSQM at Week 8 will be summarised by treatment group and domain and compared between treatments using an analysis of variance model including treatment, region and baseline vIGA-AD as factors.

14.3.7.2 Efficacy over time

To further explore possible early onset of effect and general efficacy over time, the following endpoints will be evaluated at each scheduled assessment up to Week 6 or each week up to Week 7:

- vIGA-AD TS at each scheduled assessment until Week 6.
- EASI75 at each scheduled assessment until Week 6.
- Change in SCORAD from baseline to each scheduled assessment until Week 6.
- Change from baseline to each week through Week 1 to 7 in ADSD (weekly average for each individual symptom).
    - Reduction of worst pruritus (one of the symptoms captured in the ADSD) (weekly average) of ≥4 points from baseline to each week through Week 1 to 7 among subjects with baseline worst pruritus (weekly average) of ≥4.
- Change from baseline to each week through Week 1 to 7 in Eczema-related Sleep NRS (weekly average).
- Change in DLQI score from baseline to each scheduled assessment until Week 6.
- Reduction in DLQI of ≥4 from baseline to each scheduled assessment until Week 6 among subjects with baseline DLQI ≥4.

For the binary endpoints, the same Cochran-Mantel-Haenszel test as for the Week 8 assessment will be applied. For the continuous endpoints, the repeated measurements model already described previously for the Week 8 assessments facilitates that the p-values, treatment differences, and 95% CIs can be derived for each visit up to Week 6 (or Week 7 for the change in ADSD (weekly average for each individual symptom) and Eczema-related Sleep NRS [weekly average]).

14.3.8 Analysis of pharmacodynamics and pharmacogenomics

Exploratory analyses of biomarkers will be performed for the total population as well as by disease severity.

A summary of the results will be included in the CTR if it is available in time for this. The full set of biomarker results will be reported in an addendum report to the CTR.

14.3.9 Analysis of safety

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 MedDRA. AEs will be presented by preferred terms and primary SOC.

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

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

The number of AEs and number of subjects with each type of AEs will be tabulated by treatment group.

The severity for each type of AE will be tabulated by treatment group. Where there are several recordings of severity for a given type of AE, severity will be taken as the most severe recording for that AE.

The causal relationship to IMP for each type of AE will be tabulated by treatment group. Where there are several recordings of causal relationship to the IMP for a given type of AE, causal relationship will be taken as the most-related recording from the last report of that AE, since that is when the investigator will be in possession of most information and therefore be best able to judge causal relationship.

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

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

Adverse events of special interest will be tabulated by treatment group and listed.

AEs leading to withdrawal from trial and AEs leading to permanent discontinuation of IMP will be tabulated by treatment group and listed.

14.3.9.2 Vital signs

The change in vital signs (blood pressure, pulse, body temperature) from baseline to each visit will be summarised as mean, standard deviation, median, minimum, and maximum values for each treatment group.

14.3.9.3 Clinical laboratory evaluation

The change in each of the laboratory parameters from baseline to each visit will be summarised by visit and treatment group as mean, standard deviation, median, minimum, and maximum values.

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

14.3.9.4 Subject assessment of local tolerability

Subject assessment of local tolerability will be summarised by visit and treatment group.

14.3.10 Pharmacokinetics

A separate report will be written by the respective bioanalytical CRO and added as an addendum to the CTR.

Plasma concentrations of delgocitinib will be listed and plotted versus time since last IMP application by treatment group.

14.3.11 Interim analysis

No interim analysis is planned.

14.3.12 General principles

Unless otherwise stated, all significance tests will be 2-sided using the 5% significance level. All CIs will be presented with 95% degree of confidence.

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

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

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 analysis 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 deviation.

14.3.13 Handling of missing values

Procedures for handling of missing values are included under the sections describing the individual analyses.

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Appendix 1: Definitions of adverse events and serious adverse events

Adverse event definition

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

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavourable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures unless these were planned before the subject consented to trial participation.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 11.4.4).

Serious adverse event definition

An SAE is any untoward medical occurrence that

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation. Planned hospitalisation or planned prolonged hospitalisation do not fulfil the criteria for being an SAE but should be documented in the subject's medical record.

- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

or

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

Appendix 2: Classification of adverse events

Severity

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

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

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

Causality

The *causal relation* of the AE to the use of the IMP should be described in terms of probable, possible, or not related according to the investigator's clinical judgement. The categories are defined below.

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

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

Outcome

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

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

Note that as per the above definition, LEO 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 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 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 with the outcome “RECOVERED/RESOLVED WITH SEQUELAE” could have been classified with the outcome “RECOVERED/RESOLVED” according to the CDISC definition.

For SAEs which have stabilised and cannot be expected to recover during study or safety follow-up periods, for example chronic illnesses, the final outcome should be considered to be ‘recovered’ and a statement that the SAE has stabilised should be added to the narrative in the SAE form. Please note that the event should not be reported as ‘recovered’ on the SAE form.

Appendix 3: Trial governance considerations

Appendix 3A: Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki and CIOMS International Ethical Guidelines.
- Current version of applicable ICH GCP Guidelines.
- EU's General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

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

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

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

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

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

Appendix 3B: Informed consent process

Subjects 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 (4.8) 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 applicable.

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

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

Appendix 3C: Subject and data confidentiality

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

The investigator agrees that LEO 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. Any subject's records or datasets that are transferred to LEO will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

Trial subjects must be informed and consent to that their personal trial-related data will be used by LEO 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, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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

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

Processing of personal data on behalf of LEO requires a written agreement between LEO 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 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 has obtained the necessary authorisations for the processing of personal data collected in the trial.

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

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

Source data should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data not normally collected as a routine part of the clinical practice at the site may be entered on a worksheet. Clinical assessments/safety evaluations must be signed by medically qualified investigators.

If the worksheet does not become part of the subject's medical record, the following should as a minimum be added to the subject's medical record:

- Date(s) of conducting the informed consent process, including date of provision of subject information.
- A statement from the investigator to verify that each of the eligibility criteria are met and documented.
- Subject ID.
- The fact that the subject is participating in a clinical trial in AD including treatment arms of delgocitinib cream (1, 3, 8 0r 20 mg/g) or delgocitinib cream vehicle for 8 weeks plus 2 weeks of follow-up.
- Other relevant medical information.

Trial monitoring

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

The monitoring visit intervals will depend on the trial site's recruitment rate and the compliance of the trial site with the protocol and ICH GCP.

In order to perform their role effectively, CRAs and persons involved in quality assurance and inspections will need direct access to source data, 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 and major deviations described in the CTR.

Sponsor audits, IRB/IEC review, and regulatory agency inspections

The clinical trial will be subject to audits conducted by LEO 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 staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, verify and reproduce any records and reports that are important to the evaluation of the trial.

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

Risk assessment
In this trial, the risks to critical processes and data have been evaluated.

Risk mitigation activities for endpoints include:

- Ensuring consistent data with respect to investigator assessment of efficacy (EASI, vIGA-AD and SCORAD), all assessors will receive training and whenever possible, the efficacy assessments will be made by the same investigator at each visit for a given subject to reduce inter-rater variability.
- Ensuring subjects and investigational staff are well instructed and trained about the use of the eDiary and the eDevice which will be used to collect the PROs (ADSD, Eczema-related Sleep NRS, POEM, DLQI, PGI-S, SF-36, EQ-5D-5L, WLQ, and TSQM).
- Ensuring investigational staff are well instructed and trained in collecting biomarker samples.
- Ensuring administration of IMP is controlled and documented at the site. This will be done by providing training and clear instructions to trial sites.
- Ensuring that trial sites are well trained in safety procedures such as collection and reporting of adverse events.

Throughout the trial, data quality review meetings will be held to ensure that data collections can be improved and mistakes prevented. During monitoring visits to the trial sites, the CRAs will verify that investigators work according to the protocol.

Data handling
Data will be collected by means of electronic data capture unless transmitted to LEO or designee electronically (e.g. laboratory data). The investigator or staff authorised by the investigator will enter subject data into eCRFs. Data recorded in the eCRFs will be accessible

to the trial site and LEO personnel immediately after entry. The eCRFs must be maintained in an up-to-date state by the trial site at all times.

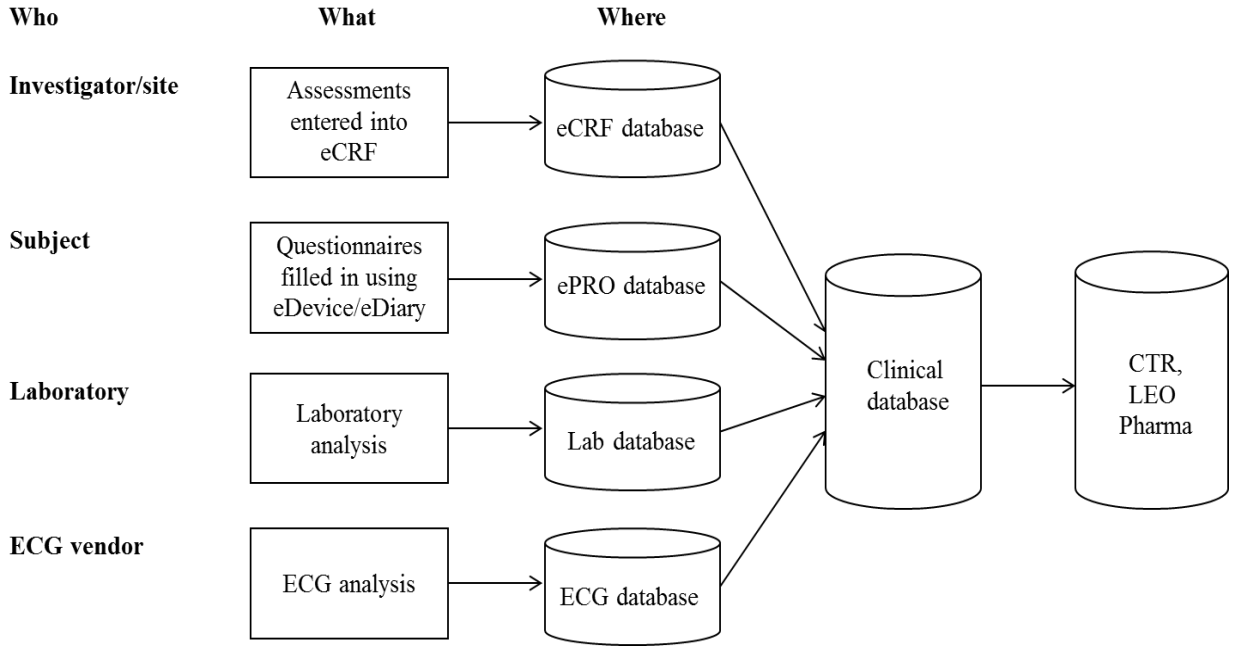
The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRFs used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original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

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

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

External data transfers from vendors to LEO will be transmitted and handled via a secure file transfer protocol site. Transmissions of electronic data from external data providers and of ePRO data to the clinical database are illustrated in Panel 14.

Panel 14: Transmission of electronic data



Abbreviations: CTR, clinical trial report; ECG, electrocardiogram; eCRF, electronic case report form; ePRO, electronic patient-reported outcome

Archiving of trial documentation

The investigator at each trial site must make arrangements to store the essential trial documents, including the investigator trial file (EU Directive 2001/20/EC). Essential trial documents must be stored until LEO informs the investigator that the documents are no longer to be retained, or longer if required by local regulations.

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

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

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

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

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

Appendix 3E: Registration, reporting and publication policy

Trial disclosure

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

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

Results of this clinical trial will be posted on the corporate website of LEO in accordance with its 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.

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

Publications

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

A multi-centre publication will be submitted for publication within 18 months after the clinical trial has been completed or terminated at all trial sites and all data have been received, defined as database lock of the clinical trial. After such multi-centre publication is made public, or if no multi-centre publication has been submitted with the above-described deadline, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements:

Prior to submission for publication or presenting a manuscript relating to the clinical trial, the investigator shall provide to LEO a copy of all such manuscripts and/or presentations. LEO shall have rights to review and comment. The investigator shall consider comments by LEO but is not required to modify the manuscript and/or presentation based on such comments,

provided, however, that the investigator upon the request of LEO 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 withhold the publication or presentation to allow LEO to protect its inventions and other intellectual property rights described in any such manuscripts.

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

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

Any publication must comply with GPP3 standards.

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

Appendix 3F: Insurance

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

Appendix 3H: Trial and site closure

Premature termination of trial or trial site

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

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

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

Reasons for the early closure of a trial site by LEO 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's 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 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 3I: Responsibilities

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

The national coordinating investigators are responsible for national issues relating to the clinical trial as agreed to in a National Coordinating Investigator Agreement.

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

Appendix 4: Short version of eligibility criteria

This appendix provides a short form (maximum 200 characters) of each of the eligibility criteria to be used when data are submitted to regulatory authorities in CDISC format.

No.	Inclusion criteria
1	Signed and dated informed consent has been obtained prior to any protocol related procedures.
2	Age 18 years and above.
3	Diagnosis of AD as defined by the Hanifin and Rajka criteria for AD (Hanifin & Rajka 1980).
4	History of AD for 1 year or more.
5	AD involvement of 5–50% treatable body surface area at screening and at baseline (excluding scalp).
6	Disease severity graded as mild to severe according to vIGA-AD (i.e. vIGA-AD of 2 or more) at screening and at baseline.
7	Able and willing to follow trial procedures including application of IMP to all AD lesions.
8	A woman of childbearing potential must use a highly effective form of birth control throughout the trial and at least for 2 weeks after last application of IMP.

No.	Exclusion criteria
1	AD lesion(s) on scalp at screening and/or baseline.
2	Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, rosacea, urticaria, or psoriasis.
3	Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD.
4	Use of tanning beds or phototherapy (NBUVB, UVB, UVA1, PUVA) within 4 weeks prior to baseline.
5	Systemic treatment with immunosuppressive/modulating drugs or corticosteroids within 4 weeks prior to baseline or 3 or more bleach baths any week within 4 weeks prior to baseline.
6	Treatment with TCSs, TCIs, topical PDE-4 inhibitors, or oral antibiotics within 2 weeks prior to baseline.
7	Change in systemic antihistamine therapy within 2 weeks prior to baseline i.e. the subjects must not start antihistamine treatment or change the current dosage regime within 2 weeks prior to baseline.
8	Receipt of live attenuated vaccines 4 weeks prior to baseline.
9	Receipt of blood products within 4 weeks prior to screening.
10	Treatment with any marketed or investigational biologic agents within 6 months or 5 half-lives prior to baseline, or until cell counts return to normal, whichever is longer.
11	Treatment with any non-marketed drug substance within the last 4 weeks prior to baseline or 5 half-lives, whichever is longer.
12	History of any active skin infection within 1 week prior to baseline.
13	A helminth parasitic infection within 6 months prior to screening that has not been treated with, or has failed to respond to, standard of care therapy.
14	Clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to baseline.
15	Tuberculosis requiring treatment within the 12 months prior to screening and/or subjects with a positive blood test for tuberculosis at screening (subjects with high risk of latent tuberculosis must be tested).

16	History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications.
17	Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.
18	History of cancer.
19	Any disorder, which is not stable, and in the investigator's opinion could affect the safety of the subject, influence the results of the trial or impede the subject's ability to complete the trial.
20	Any abnormal finding, which in the investigator's opinion may put the subject at risk, influence the results of the trial or influence the subject's ability to complete the trial.
21	Positive HBsAg, HBsAb, HBcAb or hepatitis C virus serology at screening. Subjects with positive HBsAb may be randomised provided they are hepatitis B vaccinated and have negative HBsAg and HBcAb.
22	Alanine aminotransferase or aspartate aminotransferase level 2.0 times the upper limit of normal range or more at screening.
23	Known or suspected hypersensitivity to any component(s) of the IMP.
24	Current participation in any other interventional clinical trial.
25	Previous randomisation in this clinical trial.
26	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.
27	Employed at the trial site or directly involved with the planning or conduct of the trial, or immediate family members of such individuals.
28	Legally institutionalised.
29.	Pregnant or lactating.

Appendix 5: Contact list

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

Sponsor

LEO Pharma A/S (referred to as 'LEO' 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

Appendix 6: Hanifin and Rajka (1980) diagnostic criteria for AD

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

Must have 3 or more basic features:

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

Plus 3 or more minor features:

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

Appendix 7: Protocol amendment history

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

Amendment 1 (09-Jan-2019)

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

Overall rationale for the amendment

The main reason for the amendment is to address comments to the protocol received from the US Food and Drug Administration. Miscellaneous other changes/updates have also been implemented.

The table below summarises changes made in each section and a brief rationale for each change.

Section no. and name	Description of change	Brief rationale
Section 1 Protocol synopsis	Change of treatment success abbreviation from vIGA-AD 0/1 to vIGA-AD TS. Patient Global Impression of Change (PGI-C) has been added to the list of subject assessments of efficacy and health-related quality of life; PROs. Subject assessment of local tolerability has been added as a safety assessment. Revision of exclusion criterion on tuberculosis to also include subjects with a positive blood test for tuberculosis at screening. Subjects with high risk of latent	To reflect changes in the protocol.

Section no. and name	Description of change	Brief rationale
	tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested.	
Section 4 Schedule of trial procedures	Assessment of PGI-C added. Assessment of vital signs (including body temperature) added at Visits 4, 5, 6, and 7. Tuberculosis test added.	Added as a PRO anchor scale to generate a threshold for improvement that represents a meaningful amount of change in the target population. To include an active assessment for infection at all on-site visits. To reflect that subjects with high risk of latent tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested.

Section no. and name	Description of change	Brief rationale
	Subject assessment of local tolerability added.	Added to have an active subject assessment of local tolerability (stinging/burning) in the trial.
	AD lesions on scalp changed to New AD lesions and procedure added at Visit 3 and deleted at Visit 9.	To correct inconsistency between protocol text and eCRF and to reflect how data is captured in the eCRF.
	Change to footnote on medical history.	To clarify that it is not the intention that full medical history is to be recorded both at screening and at baseline.
	Addition of footnote on WLQ.	To clarify that only subjects with a paid job are to answer the WLQ.
Section 6 Trial objectives and endpoints	Change of treatment success abbreviation from vIGA-AD 0/1 to vIGA-AD TS.	To avoid misunderstandings between a vIGA-AD score of 0 (clear) or 1 (almost clear) and vIGA-AD treatment success defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement.
	The endpoint Change in PGI-S from baseline to Week 8 has been deleted.	Due to an update of the wording of the PGI-S questionnaire (see Section

Section no. and name	Description of change	Brief rationale
		11.7.1.5), the sample size for the updated PGI-S will likely not be sufficient to perform a statistical analysis. PGI-S will still be summarised descriptively and used as an anchor scale.
Section 8.3 Exclusion criteria	Revision of exclusion criterion 15 to also include subjects with a positive blood test for tuberculosis at screening. Subjects with high risk of latent tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested.	To further safeguard subjects in risk of (re)activation of latent tuberculosis.
Section 9.7 Prohibited medication and procedures	Bleach baths have been added to list of prohibited medication and procedures (prohibited from 4 weeks prior to baseline to end of trial). Wet wraps have been added as an example of topical treatments (drug, non-drug) not allowed on lesional skin.	To clarify that bleach baths are not allowed. To provide example of topical treatments not allowed.

Section no. and name	Description of change	Brief rationale
Section 10.2.1 Reasons for discontinuation of IMP	Two new criteria for discontinuation of IMP have been added: Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status. Lymphopenia (lymphocytes <0.5x10^9/l; grade 3 according to CTCAE v5.0) confirmed by repeated measurement within 7 days.	To further safeguard subjects in case of opportunistic infections and/or lymphopenia.
Section 11.1 Overview	Panel 6 has been revised: "Investigator assessments" has been changed to "Efficacy assessments by the investigator". Box with text: "Baseline visit (Day 1) only: Check capping limits in IRT before randomization" has been deleted. "Safety and laboratory assessments" has been changed to "Safety assessments by the investigator". A new box after "Safety assessments by the investigator" has been added: "Subject assessment of local tolerability".	For clarification. Capping check will not be done in IRT but will be done by LEO Pharma A/S. For clarification. To reflect that subject assessment of local tolerability is added to the trial and that assessment

Section no. and name	Description of change	Brief rationale
		should be performed after safety assessments by the investigator.
	"Other assessments" has been changed to "Laboratory and other assessments".	For clarification.
Section 11.4.4 Laboratory testing	Panel 11 (Clinical laboratory tests):	
	Interferon gamma release test has been added.	Added to test for tuberculosis in subjects with high risk of latent tuberculosis.
	C-reactive protein has been added.	Added as an active assessment for infection.
Section 11.4.5 Subject assessment of local tolerability	New section.	Added to have an active subject assessment of local tolerability (stinging/burning) in the trial.
Section 11.6.3 Skin biopsies and photographs (all sites, but optional)	It has been added that biopsies will not be taken if the investigator considers the procedure unsuitable for the subject (e.g. subjects receiving anticoagulant therapy).	To clarify that biopsies are only to be taken if the procedure is suitable for the subject.
	It has been deleted that no further biopsies will be taken after biopsies from 100 subjects have been obtained.	The data from the analysis of the biopsies will after completion of this trial be shared with the Innovative Medicines Initiative (IMI) consortium, BIOMAP. In

Section no. and name	Description of change	Brief rationale
		order to generate robust data on AD baseline characteristics a larger dataset is needed. BIOMAP will most likely need full transcriptomics dataset for their disease characterisation. For this reason, some of the biopsies (biopsies obtained at baseline) will undergo transcriptomics profiling.
Section 11.7.1 Patient-reported outcomes (PROs)	PGI-C added to the list of PROs to be completed in the electronic device by the subjects. The number of PROs to be completed has changed from 7 to 8.	To reflect the addition of PGI-C assessment in the trial.
Section 11.7.1.5 Patient Global Impression of Severity (PGI-S)	Wording of PGI-S questionnaire has been updated.	As per advice from the US Food and Drug Administration.
Section 11.7.1.6 Patient Global Impression of Change (PGI-C)	New section.	To reflect the addition of PGI-C assessment in the trial.
Section 11.7.1.9 Work Limitation Questionnaire (WLQ)	It has been added that the WLQ will be completed at the trial site for subjects with a paid job.	To clarify that only subjects with a paid job are to answer the WLQ.

Section no. and name	Description of change	Brief rationale
Section 11.8 Estimate of total blood volume collected	The total volume to be drawn has been changed from approximately 35 mL to approximately 39 mL.	Total volume of blood needed by laboratory has been revised.
Section 11.10 Storage of biological samples	Skin swabs will also be stored in biobank and has been added to the biobank section.	Skin swabs were by mistake not mentioned in relation to biobanking in the original protocol.
Section 14.3.1 Disposition of subjects	The sentence on presentation of reasons for permanent discontinuation of IMP and withdrawal from trial has been revised. Reasons will not be presented by last visit attended.	Reasons for permanent discontinuation of IMP and withdrawal from trial will be presented by treatment group only.
Section 14.3.4 Testing strategy Section 14.3.6 Analysis of secondary efficacy endpoints Section 14.3.7.2 Efficacy over time	Change of treatment success abbreviation from vIGA-AD 0/1 to vIGA-AD TS.	To avoid misunderstandings between an vIGA-AD score of 0 (clear) or 1 (almost clear) and vIGA-AD treatment success defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement.
Section 14.3.7.1 Analysis of patient-reported outcomes	PGI-C has been added to the list of PROs to be summarised by treatment group and visit using descriptive statistics. Time interval calculations of weekly average of ADSD have been revised (e.g. baseline weekly average of ADSD will be defined	To reflect the addition of PGI-C assessment in the trial. The approach for calculation of weekly average has been revised since ADSD is completed in the evening

Section no. and name	Description of change	Brief rationale
	by average of measurements from Day -7 to Day -1 instead of from Day -6 to Day 1) and text has been slightly revised. The description of how to analyse PGI-S has been deleted.	throughout the trial. PGI-S has been deleted as an endpoint and will only be summarised descriptively.
Section 14.3.9.1 Adverse events	It has been added that adverse events of special interest will be tabulated by treatment group and listed. AEs leading to withdrawal from trial and AEs leading to-permanent discontinuation of IMP will be tabulated by treatment group. No narratives will be made for these AEs.	To clarify how adverse event of special interest will be summarised. AEs leading to withdrawal from trial and AEs leading to permanent discontinuation of IMP, as well as AEs of special interest will be tabulated and listed as this is a more informative way of presenting data on these event types.
Section 14.3.9.4 Subject assessment of local tolerability	New section.	To describe statistical handling of the subject assessment of local tolerability.
Appendix 4 Short version of eligibility criteria	Revision of exclusion criterion 15 to also include subjects with a positive blood test for tuberculosis at screening (subjects with high	To further safeguard subjects in risk of (re)activation of latent tuberculosis.

Section no. and name	Description of change	Brief rationale
	risk of latent tuberculosis must be tested).	
Throughout	Minor editorial and document formatting changes.	Minor, have therefore not been summarised.

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