Dermatology
beyond the skin

Cover Page

Official title: Efficacy and safety of twice-daily application of delgocitinib cream 20 mg/g for 6 weeks in subjects with active discoid lupus erythematosus. A phase 2a exploratory, randomised, double-blind, vehicle-controlled, within-subject, multi-centre trial.
LEO Pharma number: EXP-1373
NCT number: NCT03958955
Date: 22-Oct-2019

Clinical Trial Protocol

EXP-1373

Efficacy and safety of twice-daily application of delgocitinib cream 20 mg/g for 6 weeks in subjects with active discoid lupus erythematosus

A phase 2a exploratory, randomised, double-blind, vehicle-controlled, within-subject, multi-centre trial

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

LEO Pharma A/S	**Trial ID:**	**EXP-1373**
	Date:	**22-Oct-2019**
	EudraCT no:	**2018-003615-22**
	Version:	**4.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

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

PPD , MSc
Biostatistics Lead, Medical Sciences

PPD , MD
Vice President, Medical Sciences

PPD , PhD
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:

Margitta Worm, Univ. Prof. Dr. Med
Signatory investigator

Acknowledgement statement investigator(s)

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

Protocol amendment summary of changes table

Document history

Document	Date	Type of protocol amendment
Amendment 2 (substantial) (version 4.0)	22-Oct-2019	Global
Amendment 1 (substantial) (version 3.0)	15-May-2019	Global
Original protocol (version 2.0)	22-Feb-2019	NA

Note that the protocol amendment summary of changes table for the previous amendment is located in Appendix 9.

Amendment 2 (22-Oct-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 protocol is amended to address recruitment issues. DLE is a rare disease, and the number of patients eligible for this trial is very limited. The exclusion criteria concerning tobacco use and hepatitis B serology have been modified to ease recruitment without compromising the safety of the subjects and the evaluation of trial results.

Subjects who are in screening when this amendment is approved will be re-assessed for eligibility according to the amended eligibility criteria.

All changes to the protocol are summarised below.

Section no. and name	Description of change	Brief rationale
8.3 Exclusion criteria (also protocol synopsis and Appendix 4)	Exclusion criterion no. 17 was changed from a pre-defined limit (>70 cigarettes/week or >70 g tobacco/week) to instead exclude subjects with unstable or fluctuating use of tobacco.	To allow randomisation of subjects smoking >10 cigarettes/day. Tobacco may affect the course of DLE and thus the trial results, but as long as the tobacco use is stable for at least 1 month prior to screening, the actual consumption is considered less important.
	Exclusion criterion no. 26 was modified to only exclude positive human immunodeficiency virus antibody, hepatitis B surface antigen, and hepatitis C virus antibody serology (and not positive hepatitis B surface antibody and hepatitis B core antibody serology).	Reactivation of hepatitis B is considered only a theoretical risk, as the treatment is topical and only applied to a very small area (≤1% of BSA), and therefore the systemic exposure is negligible. Furthermore, subjects will not be randomised if they have signs of active infection, and randomised subjects will be monitored for signs of active infection during the trial.
Section 11.5.2 Non-invasive skin sampling	It was added that non-invasive skin sampling will not be done for subjects who have plaster or bandage allergy.	To avoid allergic reactions to the adhesive patches used for non-invasive skin sampling.
Appendix 9 Protocol amendment history	New appendix added containing the summary of the previous protocol amendment.	To document the protocol amendment history, and to keep only the most recent amendment summary at the start of the protocol.
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarised.

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List of panels

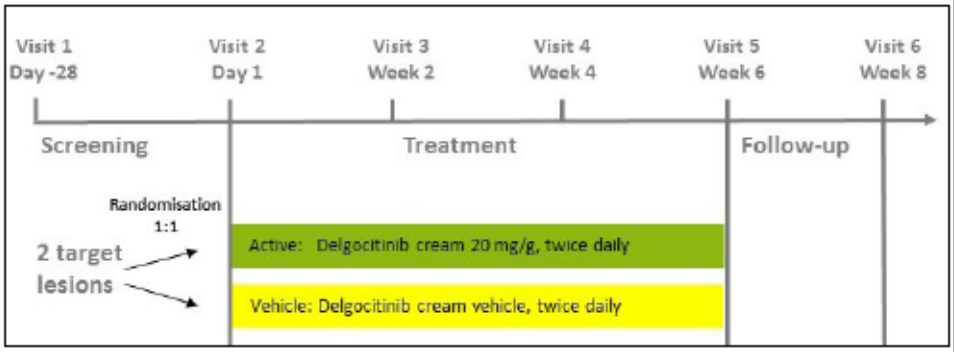
List of abbreviations

ACR	American College of Rheumatology
AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BSA	body surface area
CDISC	Clinical Data Interchange Standards Consortium
CHE	chronic hand eczema
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLE	cutaneous lupus erythematosus
CMO	contract manufacturing organisation
CRA	clinical research associate
CRO	contract research organisation
CTR	clinical trial report
CXCL	chemokine (C-X-C motif) ligand
DLE	discoid lupus erythematosus
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
GCP	Good Clinical Practice
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IEC	independent ethics committee
IFN	interferon
IGA	Investigator's Global Assessment
IL	interleukin
IMP	investigational medicinal product

IRB	institutional review board
IRT	interactive response technology
JAK	janus kinase
LE	lupus erythematosus
MedDRA	Medical Dictionary for Regulatory Activities
PaGA	Patient's Global Assessment
PDE-4	phosphodiesterase-4
PP	per protocol
RCLASI	Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index
SAE	serious adverse event
SD	standard deviation
SLE	systemic lupus erythematosus
SOC	system organ class
SPF	sun protection factor
STAT	signal transducer and activator of transcription
Th	T helper
UV	ultraviolet

1 Protocol synopsis

<table>
<tr><td>Trial ID
EudraCT no.</td><td>EXP-1373
2018-003615-22</td></tr>
<tr><td>Title of trial</td><td>Efficacy and safety of twice-daily application of delgocitinib cream 20 mg/g for 6 weeks in subjects with active discoid lupus erythematosus.
A phase 2a exploratory, randomised, double-blind, vehicle-controlled, within-subject, multi-centre trial.</td></tr>
<tr><td>Short title of trial</td><td>Effect and safety of delgocitinib cream in discoid lupus erythematosus.</td></tr>
<tr><td>Main objectives and endpoints</td><td>
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary objective</td><td>Primary endpoint</td></tr>
<tr><td>To investigate the efficacy of delgocitinib cream 20 mg/g twice daily on active discoid lupus erythematosus (DLE) target lesions.</td><td>• Target lesions with Investigator's Global Assessment (IGA)[a] score of 0 or 1 at Week 6.</td></tr>
<tr><td>Secondary objective</td><td>Secondary endpoints</td></tr>
<tr><td>To evaluate the safety of delgocitinib cream 20 mg/g twice daily on active DLE target lesions.</td><td>• Adverse events (number of AEs and number of subjects with AEs) up to Week 6.
• Number of lesion-specific, treatment-related AEs up to Week 6.</td></tr>
<tr><td>To further investigate the efficacy of delgocitinib cream 20 mg/g twice daily on active DLE target lesions.</td><td>• A ≥2-point reduction in IGA score at Week 6 compared to baseline.
• A ≥2-point reduction in erythema score[b] at Week 6 compared to baseline.
• Erythema score at Week 6.
• Total skin disease activity score (sum of scores for erythema, scaling/hyperkeratosis, and oedema/infiltration)[b] at Week 6.</td></tr>
</table>
a) The IGA is an instrument used in this clinical trial to rate the severity of the subject's DLE target lesions on a 5-point scale ranging from 0 (clear) to 4 (severe).
b) The disease activity scores are based on the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) and the Revised CLASI (RCLASI) which are validated scoring systems to assess disease activity and damage in patients with cutaneous lupus erythematosus.
Abbreviation: AE = adverse event.
</td></tr>
</table>

Final collection of data for the primary endpoint	Week 6.
Trial design	This is a phase 2a multi-centre, double-blind, randomised, within-subject, vehicle-controlled trial. Each subject must have at least 2 active DLE target lesions of at least moderate severity. The target lesions will be randomised 1:1 to treatment with delgocitinib cream 20 mg/g or vehicle twice daily for 6 weeks. The trial consists of a screening period, a treatment period, and a follow-up period.  <u>Screening period</u> The screening period has a duration of up to 4 weeks. At the screening visit, the subjects' eligibility to enter the trial will be checked. For each subject, 2 potential DLE target lesions will be identified and evaluated. Blood and urine samples will be taken for safety laboratory analysis, and an electrocardiogram (ECG) will be recorded. Furthermore, the subjects will be asked to fill out the Dermatology Life Quality Index (DLQI). <u>Treatment period</u> At baseline (Day 1), the eligibility of the subjects and their target lesions will be confirmed. For eligible subjects, the 2 target lesions will be randomised 1:1 to treatment with delgocitinib cream or vehicle. The first application of the investigational medicinal products (IMPs) will occur at baseline at the trial site. The subsequent IMP applications will be performed by the subjects at home twice daily for 6 weeks. During the treatment period, the subjects will be required to return to the trial site for visits scheduled at Weeks 2, 4, and 6. The last IMP applications will occur the evening before the subjects attend the visit scheduled at Week 6. <u>Safety follow-up period</u> All subjects will attend a safety follow-up visit 2 weeks after the last IMP applications.

Main assessments	Investigator efficacy assessments: • IGA of each target lesion. • Skin lesion activity and damage scores: erythema, scaling/hyperkeratosis, oedema/infiltration, dyspigmentation, scarring/atrophy (based on components of the CLASI and RCLASI) for each target lesion. Subject assessments of efficacy and health-related quality of life: Patient's Global Assessment (PaGA) of severity of each target lesion. Safety assessments: Vital signs, physical examination, safety laboratory tests, and adverse event reporting.
Main criteria for inclusion	• Age 18-70 years. • Histopathological findings (current or previous) consistent with clinical diagnosis of DLE. • Unequivocal clinical diagnosis of 2 active DLE target lesions that are <6 months old and amenable for clinical evaluation. This includes lesions located on the scalp if they fulfil all lesion-specific eligibility criteria. • Target lesion IGA score of at least moderate severity (≥3) at screening and baseline. • Target lesion erythema score ≥2 at screening and baseline.
Main criteria for exclusion	• Target lesion dyspigmentation score of 2 at screening or baseline. • Target lesion scarring/atrophy score of 2 at screening or baseline. • Target lesion scarring alopecia score of >0 in scalp lesions at screening or baseline. • Medical history of systemic lupus erythematosus (SLE) with clinically significant organ involvement (American College of Rheumatology SLE classification criteria no. 6 to 9) including SLE-related pleuritis or pericarditis (by clinical evaluation and electrocardiogram), and neurologic, renal, and/or other major SLE-related organ system involvement. SLE joint involvement is acceptable. • Subjects with unstable or significant SLE disease activity findings that would, by its progressive nature and/or severity, interfere with the trial evaluation, completion, and/or procedures per the investigator's discretion. • Other skin conditions at screening or baseline that would interfere with the evaluation of DLE. • Immunosuppressive/immunomodulating therapy with e.g. methotrexate, cyclosporine, azathioprine, retinoids (both topical and systemic), or dapsone within 4 weeks prior to baseline. • Systemic prednisolone >7.5 mg/day or changed dose within 4 weeks prior to baseline (nasal and inhaled corticosteroids are allowed). • Treatment with the following medications: • Oral antimalarial treatment with hydroxychloroquine >6.5 mg/kg body weight/day, or chloroquine >4 mg/kg body weight/day, or changed dose within 12 weeks prior to baseline.

	• Quinacrine combined with either hydroxychloroquine or chloroquine within 12 weeks prior to baseline. • Drugs known to interact with antimalarials (e.g. digoxin, cimetidine) within 12 weeks prior to baseline. • Treatment with topical corticosteroids, calcineurin inhibitors, and phosphodiesterase-4 (PDE-4) inhibitors within 2 weeks prior to baseline. • Use of systemic antibiotics or cutaneously applied antibiotics on the target lesions within 2 weeks prior to baseline. • Ultraviolet (UV) therapy within 2 weeks prior to baseline. • Any procedure impairing the skin barrier (e.g. incision) within 2 cm from the border of any of the target lesions within 4 weeks prior to baseline. • Receipt of live (attenuated) vaccines within 4 weeks prior to baseline. • Treatment with any marketed biological therapy or investigational biologic agents: • 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. • Unstable or fluctuating use of tobacco within 1 month prior to screening which, in the opinion of the investigator, may affect the natural course of the disease and thus affect the evaluation of the treatment. • History of any active skin infection within 1 week prior to baseline. • 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 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 at screening.
Investigational medicinal products	• Name of IMP: delgocitinib cream. • Active substance: delgocitinib. • Formulation: cream. • Formulation strength: 20 mg/g and vehicle. • Dose and method of administration: topical application twice daily.

Duration of treatment	6 weeks.
Number of subjects	This trial aims to have 36 subjects evaluable for the primary endpoint. Assuming a drop-out rate of 20%, approximately 45 subjects will be randomised to achieve this.
Number and distribution of trial sites	Approximately 20 sites in several countries in the EU and/or United States.
Statistical methods	<u>Primary endpoint:</u> The efficacy of delgocitinib cream compared with vehicle will be analysed in a within-subject comparison of lesion-specific treatment success (defined as an IGA score of 0 or 1 at Week 6) using McNemar's test. <u>Secondary endpoints:</u> Within-subject comparisons of the numbers of AEs, subjects with AEs, and treatment-related, lesion-specific AEs will be done by treatment using a Wilcoxon signed rank test. Within-subject comparisons of lesion-specific binary endpoints to assess treatment difference at Week 6 will be done by McNemar's test. Within-subject comparisons of lesion-specific disease activity scores to assess treatment difference at Week 6 will be done by a Wilcoxon signed rank test. The analysis of the primary and secondary endpoints will be performed on the per protocol analysis set and repeated for the full analysis set as a sensitivity analysis.
Signatory investigator	Margitta Worm, Univ. Prof. Dr. Med. Department of Dermatology, Venereology and Allergology, Campus Charité Mitte, Berlin, Germany
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark.

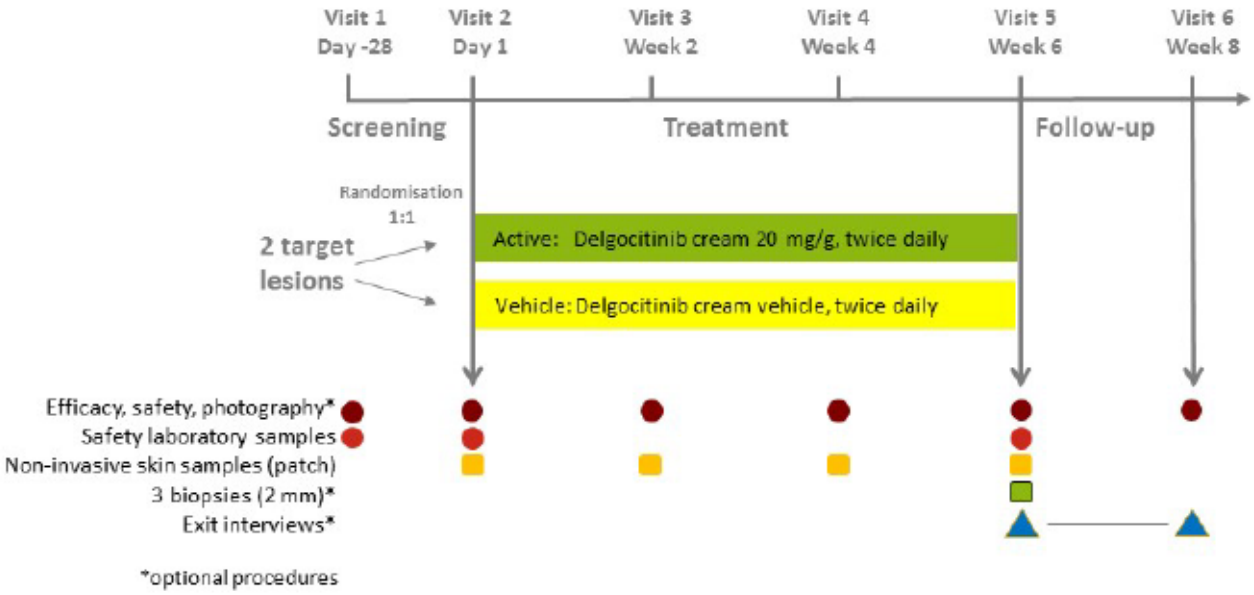
2 Trial identification

EudraCT number: 2018-003615-22.

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

3 Schematic of trial design

Panel 1: Trial design



4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

	Screening[a]	Treatment				Follow-up	Uns. visit (if applicable)	Early term. (if applicable)[c]	Primary endpoint visit (if applicable)[d]	References (protocol section)
Visit	1	2	3	4	5	6				
Day/Week	Day -28 to -7	Day 1	Week 2	Week 4	Week 6	Week 8	-	-	Week 6	
Visit window (days)[b]	-28 to -7	NA	±3	±3	±3	±3	-	-	±3	
Trial population and eligibility										
Informed consent(s)[e]	X									Appendix 3B
Subject eligibility	X	X								8.2, 8.3
IMP and randomisation										
Randomisation		X								9.3
Instruction of IMP application		X								9.2
Dispensing of IMP		X	X	X			X			9.2
Treatment compliance			X	X	X			X		9.8.3
Return of IMP			X	X	X			X		9.8.3
Concomitant medication	X	X	X	X	X	X	X	X	X	9.4, 9.6, 9.7
Concurrent procedures	X	X	X	X	X	X	X	X	X	9.6
Investigator assessments at screening/baseline only										
Demographics	X									11.2.1
Fitzpatrick skin type	X									11.2.2
Medical history[f]	X	X								11.2.3
Height and weight	X									11.2.4

	Screening[a]	Treatment				Follow-up	Uns. visit (if applicable)	Early term. (if applicable)[c]	Primary endpoint visit (if applicable)[d]	References (protocol section)
Visit	1	2	3	4	5	6				
Day/Week	Day -28 to -7	Day 1	Week 2	Week 4	Week 6	Week 8	-	-	Week 6	
Visit window (days)[b]	-28 to -7	NA	±3	±3	±3	±3	-	-	±3	
Classification of SLE (ACR endorsed criteria, 1997)	X									11.2.5
CLASI and RCLASI[g]	X	(X)								11.2.6, 11.2.7
Identification of target lesions[h]	X	X								11.2.8
Subject assessments of efficacy and health-related quality of life										
DLQI		X								11.6.1.2
PaGA	X	X	X	X	X	X		X		11.6.1.1
Investigator assessments of efficacy[i]										
IGA	X	X	X	X	X	X		X	X	11.3.1
Skin lesion activity (erythema, scaling/hyperkeratosis, oedema/infiltration)	X	X	X	X	X	X		X		11.3.2
Skin lesion damage (dyspigmentation, scarring/atrophy)	X	X	X	X	X	X		X		11.3.3
Investigator assessments of safety										
Vital signs (blood pressure, peripheral pulse, body temperature)	X	X			X		X	X		11.4.1
Physical examination	X				X		X	X		11.4.2
ECG	X						X			11.4.3
Serology (central laboratory)	X									11.4.4

	Screening[a]	Treatment				Follow-up	Uns. visit (if applicable)	Early term. (if applicable)[c]	Primary endpoint visit (if applicable)[d]	References (protocol section)
Visit	1	2	3	4	5	6				
Day/Week	Day -28 to -7	Day 1	Week 2	Week 4	Week 6	Week 8	-	-	Week 6	
Visit window (days)[b]	-28 to -7	NA	±3	±3	±3	±3	-	-	±3	
Chemistry, haematology (central laboratory)	X	X			X		X	X		11.4.4
Urinalysis (central laboratory)	X[j]	X			X		X	X		11.4.4
Urine pregnancy test	X	X		X	X	X	X	X		11.4.4
Adverse events	X	X	X	X	X	X	X	X	X	13
Other assessments										
Size of target lesions	X	X			X			X		11.6.2
Non-invasive skin sampling (patch)[k]		X	X	X	X			X		11.5.2
Skin biopsies (optional)[l]					X[m]			X[m, n]		11.5.3
Check of biopsy wound healing[o]						X				11.5.3
Exit interviews[l, p]					X			X		11.6.1.3
Photography[l]	X	X	X	X	X[m]	X		X[m]		11.6.3
End of trial form[q]						X		X	X	11.8

a) Subjects that fail to meet all eligibility criteria at screening may be re-assessed for eligibility at a later stage under certain circumstances (see Section 8.4). For these subjects, re-assessment of eligibility will be performed at an additional screening visit prior to baseline (Day 1).

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.

c) Subjects who discontinue IMP or withdraw from the trial will be asked to return to the trial site for an early termination visit as soon as possible after last IMP application (see Section 10). They will also be asked to return at Week 6 for a primary endpoint visit (see footnote d). In addition, all subjects will have a final safety follow-up visit 2 weeks after last application of IMP.

d) The primary endpoint visit is applicable to subjects who discontinue IMP prior to Week 6. The visit should be scheduled 6 weeks after the first application of IMP.
e) The informed consent form(s) must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations and wash-out of disallowed medications.
f) Medical history is to be recorded at screening. At baseline (Day 1), medical history for the selected target lesions is to be reviewed and updated, if needed (see Section 11.2.3).
g) A full, global CLASI/RCLASI assessment will be done at screening. In addition, if any of the (potential) target lesions are located in the scalp, scarring alopecia will be scored for each scalp (potential) target lesion at screening and baseline to evaluate exclusion criterion no. 3.
h) At screening, 2 potential target lesions will be identified and evaluated. At baseline (Day 1), the eligibility of the target lesions will be confirmed prior to randomisation. In the unlikely event that 1 or both lesions are no longer eligible at baseline, the investigator is allowed to select new target lesions if available (see Section 11.2.8).
i) Investigator assessments of efficacy must be done prior to or at least 2 hours after application of IMP.
j) In addition, the urine sample will be tested for proteinuria with a urine dipstick at screening (see Section 11.4.4).
k) Non-invasive skin sampling must be done prior to or at least 4 hours after application of IMP.
l) This procedure is optional and requires that the subject provides additional informed consent.
m) For subjects who consent to the skin biopsy and photography components, photographs should preferably be taken both before and after taking the biopsy at Week 6 or early termination.
n) Biopsies will only be taken at the early termination visit if the subject received treatment with the IMPs at least until the Week 2 visit.
o) Only applicable to subjects who provided skin biopsies at Week 6 or early termination.
p) Exit interviews will only be conducted in selected countries.
q) An end of trial form must be completed in the eCRF for all randomised subjects at their last visit (the early termination visit, the safety follow-up visit, or the primary endpoint visit at Week 6, whichever comes last). See Section 11.8 for further details.

Abbreviations: ACR = American College of Rheumatology; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; IGA = Investigator's Global Assessment; IMP = investigational medicinal product; PaGA = Patient's Global Assessment; RCLASI = Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index; SLE = systemic lupus erythematosus; term. = termination; uns. = unscheduled.

5 Introduction and trial rationale

5.1 Discoid lupus erythematosus

Discoid lupus erythematosus (DLE) is an autoimmune disease affecting the skin with erythematous, scaly, well-demarcated lesions. Over time, these lesions can cause scarring, atrophy, dyspigmentation, and hair loss, resulting in significant disfigurement. DLE lesions generally range in size from a few mm to 15 cm in diameter and are primarily found in ultraviolet (UV)-exposed areas such as the head and neck, and to a lesser extent on the trunk and extremities (1). The physical appearance affects the quality of life in DLE patients and is associated with increased risk of depression and unemployment (2).

DLE is one of the manifestations of lupus erythematosus (LE) which covers different disease types ranging from cutaneous to systemic involvement. In systemic LE (SLE), multiple organs including the heart, kidneys, skin, and joints may be involved. Cutaneous LE (CLE) can be either acute, subacute, or chronic, and DLE is the most common form of chronic CLE, representing 80% of all cases (2). The CLE disease types present with different clinical, histological, and serological features, and different prognoses (3).

The prevalence of CLE was estimated to 73/100.000 in an American study with a predominately white population (4). However, other studies have shown that DLE is more common in people with black skin (2, 5). DLE has a female predominance and a peak age of onset in the fourth decade in women and slightly later in men (6). DLE is categorised as either localised (only lesions above the neck) or generalised (lesions both above and below the neck), of which the localised form is far more common (7). Patients with generalised DLE are more likely to develop SLE than patients with localised DLE (8). In a Swedish cohort study, the probability for DLE patients to subsequently develop SLE was 16.7% after 3 years (9). Conversely, DLE develops during the course of SLE in 15-30% of SLE patients (10). DLE might progress to SLE more commonly in children than in adults (11).

The disease mechanism of DLE involves damage of the keratinocytes induced by UV sun light and the subsequent generation of autoantigens. This induces an inflammatory response resulting in characteristic histological features (12-14). The early inflammatory mediators include tumour necrosis factor alpha (TNF-α) and interleukin (IL)-1β which attract skin-homing T cells and plasmacytoid dendritic cells (12, 13). Exposure to the autoantigens stimulates the production of interferon alpha (IFN-α) and interferon gamma (IFN-γ) and further infiltration and activation of T helper (Th1) cells, which in turn activates the janus kinase (JAK)/signal transducer and activator of transcription (STAT) signalling pathways (15-17). The lesional tissue shows elevated levels of IFN-γ and chemokines including chemokine

(C-X-C motif) ligand (CXCL) 9, CXCL10, and CXCL11, and an increased number of autoreactive cytotoxic cluster of differentiation 8 (CD8) positive T cells (12, 15, 16). In summary, the inflammatory disease profile indicates that the JAK/STAT pathway is central for the DLE disease mechanism and may be an important therapeutic target (18).

There is currently no cure for DLE, and no treatments have been approved for this indication. The current standard-of-care treatments are used off-label and have limited effect. First-line treatment recommendations include sun avoidance, UV protection, and potent topical corticosteroids. Topical calcineurin inhibitors are also used. In severe or widespread disease, systemic antimalarials are recommended (19).

5.2 Experience with investigational medicinal product

The investigational medicinal product (IMP) in this trial is delgocitinib cream.

Delgocitinib (recently assigned as the international non-proprietary name [INN] for LEO 124249) is a pan-JAK inhibitor. Delgocitinib blocks several cytokine-mediated 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.

DLE is a new indication for delgocitinib, and no non-clinical or clinical data are available specifically for this indication. Current knowledge is mainly derived from clinical trials with delgocitinib ointment in the indications atopic dermatitis (AD) and chronic hand eczema (CHE). A compilation of non-clinical and clinical data for delgocitinib is given in the current version of the investigator's brochure.

CCI [redacted]

No clinical trials have yet been completed with delgocitinib cream. A total of 8 clinical trials (1 with delgocitinib oral formulation and 7 with delgocitinib ointment) were completed at the cut-off date for the investigator's brochure (version 2.0).

The efficacy of delgocitinib ointment was investigated in 6 trials in different indications (AD, CHE, inverse psoriasis, and alopecia areata) and was proven to be efficacious in AD and

CHE. Based on non-clinical dermal absorption studies, it is expected that delgocitinib cream will also be efficacious in these indications.

CCI [redacted]

5.3 Trial rationale

The purpose of this phase 2a trial is to build disease understanding and investigate the efficacy and safety of delgocitinib cream in the treatment of subjects with active DLE lesions. In addition, the trial will include qualitative patient interviews to explore the signs, symptoms, and impact of DLE.

DLE is a rare disease, and therefore the options to test potential new treatments are limited. To date, no treatments have been approved for DLE. The topical and systemic treatments used in DLE are used off-label and are rarely supported by evidence from randomised controlled trials (19). This constitutes an unmet medical need in the treatment of DLE.

Delgocitinib blocks both type I and type II interferons and IL-12, all of which are over-expressed in the skin of CLE patients and expected to contribute to the pathogenesis. Scientific evidence from human DLE lesions supports that the autoinflammatory process is mediated via Th1 cells and IFN-γ signalling which activate the JAK/STAT signalling pathways (12, 17). Therefore, it is expected that treatment with delgocitinib through inhibition of JAK/STAT signalling will block the inflammatory process and the associated skin signs of erythema, scaling, and infiltration. This is supported by non-clinical evidence that the JAK inhibitor ruxolitinib prevented development of skin lesions in mice prone to develop spontaneous CLE and SLE (20). The treatment is not expected to reverse pre-existing skin damage caused by DLE.

CCI [redacted]

CCI [redacted]

As an exploratory component of this trial, exit interviews will be conducted with a subgroup of subjects to gain insight into the patient experience of DLE (signs, symptoms, and impact on different domains of health-related quality of life [HRQoL]) and to help inform the selection and development of patient-reported outcomes and other endpoints for future trials. The subjects' experiences (positive and negative) with the IMP and the trial procedures will also be explored.

5.4 Ethical considerations

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and in compliance with the approved protocol and applicable regulatory requirements.

No children, adolescents, or other vulnerable subjects incapable of giving informed consent will be enrolled in this clinical trial. Furthermore, women who are pregnant, breastfeeding, or trying to become pregnant will not be enrolled in this clinical trial. Women of childbearing potential must agree to use a highly effective method of contraception to prevent pregnancy during the clinical trial. In addition, all female subjects of childbearing potential will have a pregnancy test performed before and during the trial, and at end of treatment and safety follow-up to ensure that no foetuses are exposed to the IMP. No contraceptive measures are required for male subjects exposed to delgocitinib cream as no or negligible systemic absorption is expected.

Eligible subjects with 2 active DLE lesions (target lesions) will be randomised to treatment with delgocitinib cream 20 mg/g and vehicle to each of the target lesions. Thus, all trial subjects will receive active treatment on 1 DLE lesion twice daily for 6 weeks. This treatment duration is expected to be sufficient to induce significant improvement in the disease activity. The choice of a vehicle control and the within-subject trial design is considered appropriate for addressing the objectives of this trial. Based on evidence from a previous within-subject trial in a similar patient population, there are no concerns that vehicle treatment of 1 target lesion for the duration of the trial will cause permanent skin damage from DLE (21). For the same reason, it is also considered ethically justified to prohibit other topical DLE treatments during the treatment phase to avoid accidental use of these on the target lesions. The

within-subject trial design reduces the required sample size by eliminating the between-subject variation. Reducing the required number of subjects is considered very important for recruitment due to the low number of eligible patients with this rare disease.

DLE lesions can range in size from few mm to 15 cm in diameter (i.e. up to 1% of total BSA) (1), but the expected average size of DLE lesions is approximately 2 cm^2 for non-scalp lesions and 6 cm^2 for scalp lesions (22). Due to the small treatment area, the risk of systemic exposure and side effects in this trial is considered very low. See Section 5.2 for further information regarding non-clinical and clinical data for delgocitinib.

In accordance with the current version of the ICH-GCP guidelines, medically qualified personnel employed by LEO will be readily available to advise on trial-related medical questions. Medical monitoring will be performed throughout the trial, and safety data will be reviewed regularly by medically qualified staff at LEO to ensure that prompt action is taken, if needed, to maximise patient safety.

Although safety measures are taken to mitigate any risk, AEs may occur. To ensure the safety and well-being of the subjects, AEs will be carefully monitored throughout the trial by trained site staff and investigators. Moreover, subjects will undergo physical examinations and safety lab evaluations to ensure that their overall health is in accordance with the eligibility criteria of the trial and to detect any AEs.

During the informed consent process, it will be made clear which components of the trial that are optional and what these components include. This concerns the exit interviews (only conducted in selected countries), photography, and skin biopsies.

5.5 Benefit/risk assessment

Detailed information about known and expected benefits and risks, reasonably expected AEs, contraindications, and special warnings associated with delgocitinib are summarised in the investigator's brochure.

There is an unmet medical need for new topical treatments for patients with DLE, as there is no approved treatment for this indication, and the current off-label treatment options have associated limitations in terms of efficacy and/or safety. The potential benefit for the subjects participating in this trial is the possibility of receiving an efficacious treatment on 1 active DLE lesion. The relative importance of this benefit will depend on the extent and total number of DLE lesions in the trial subject (the mean number of DLE lesions per subject is

expected to be between 2.6 and 4.3 (22, 23)). All subjects will undergo a thorough medical check-up as part of the trial which may also be seen as a benefit.

The risk associated with participating in this trial is considered low. No important identified risks have been documented during the overall non-clinical and clinical development of delgocitinib to date. Based on this, the new cream formulation is expected to be safe and well tolerated. In this trial, the maximum expected treatment area is 1% of BSA, and the recommended dose is 0.3 g of delgocitinib cream 20 mg/g per 1% BSA. The treatment area and the amount of IMP to be applied are well below the maximum treatment area and daily dose of delgocitinib applied in previous clinical trials with delgocitinib ointment. For example in 1 previous trial, a mean BSA of 36% was treated with 10 g of delgocitinib ointment 30 mg/g per day. Therefore, no systemic effects are expected in this trial. Treatment with delgocitinib ointment has caused no severe AEs in previous trials, and mild and moderate reactions have resolved after end of treatment. No local allergic reactions are expected. However, despite good knowledge of the IMP, introducing a new formulation in a new indication may cause yet unknown AEs. The risk to the subjects will be minimised by ensuring that they fulfil all eligibility criteria and by close medical monitoring.

There is a risk that some of the subjects' DLE lesions will get worse during the trial, as 1 target lesion will be treated with vehicle, and topical treatment of other DLE lesions is prohibited during the trial. However, any permanent damage from this is considered very unlikely in this short trial.

The safety of the subjects will be monitored as described in Section 11.4. The risks associated with the invasive procedures in this trial (blood sampling and skin biopsies) are considered minimal. Blood sampling is considered a low risk procedure. Skin biopsies are optional for the subjects. The size of the skin biopsies should not necessitate suturing, but suturing can be performed at the investigator's discretion. A check of skin biopsy wound healing including removal of suture, if applicable, will be performed at the following visit. The risk associated with a skin biopsy, including secondary infection and scarring, is considered low.

In conclusion, the conduct of this trial is considered safe and ethically justified. The associated risk is low and outweighed by the benefit of a potential future treatment for DLE, which is a rare disease with an unmet need for treatment.

6 Trial objectives and endpoints

Panel 3: Objectives and endpoints

Objectives	Endpoints
Primary objective	Primary endpoint
To investigate the efficacy of delgocitinib cream 20 mg/g twice daily on active DLE target lesions.	• Target lesions with Investigator's Global Assessment (IGA)[a] score of 0 or 1 at Week 6.
Secondary objectives	Secondary endpoints
To evaluate the safety of delgocitinib cream 20 mg/g twice daily on active DLE target lesions. To further investigate the efficacy of delgocitinib cream 20 mg/g twice daily on active DLE target lesions.	• Adverse events (number of AEs and number of subjects with AEs) up to Week 6. • Number of lesion-specific, treatment-related AEs up to Week 6. • A ≥2-point reduction in IGA score at Week 6 compared to baseline. • A ≥2-point reduction in erythema score[b] at Week 6 compared to baseline. • Erythema score at Week 6. • Total skin disease activity score (sum of scores for erythema, scaling/hyperkeratosis, and oedema/infiltration)[b] at Week 6.
Exploratory objectives	Exploratory endpoints
To further investigate the efficacy of delgocitinib cream 20 mg/g twice daily on DLE target lesions with active disease.	• IGA score at Weeks 2, 4, and 6. • Patient's Global Assessment (PaGA)[c] score of 0 or 1 at Week 6. • A ≥2-point reduction in PaGA score at Week 6 compared to baseline. • PaGA score at Week 6. • Scaling/hyperkeratosis score[b] at Week 6. • Oedema/infiltration score[b] at Week 6. • Dyspigmentation score[b] at Week 6. • Scarring/atrophy score[b] at Week 6. • Total skin disease damage score (sum of scores for dyspigmentation and scarring/atrophy)[b] at Week 6. • Total skin lesion disease score (sum of scores for total skin disease activity and total skin disease damage)[b] at Week 6.

Objectives	Endpoints
To explore the effect of delgocitinib on DLE-related genes and biomarkers.	• Change in skin biomarker levels from baseline to Week 6. • Skin biomarker levels in delgocitinib-treated skin compared with non-lesional skin at Weeks 2, 4, and 6. • Gene expression levels in biopsies from delgocitinib-treated skin compared with vehicle-treated skin at Week 6. • Gene expression levels in biopsies from delgocitinib-treated skin compared with non-lesional skin at Week 6. • Gene expression levels in biopsies from vehicle-treated skin compared with non-lesional skin at Week 6.
To explore the signs, symptoms, and impact on health-related quality of life of DLE, and gain insight into the subject experience with the IMP and trial procedures.	• Qualitative, semi-structured exit interviews after end of treatment to gain qualitative insight into the patient experience of DLE, and the experience of the IMP and the participation in the clinical trial.

a) In this trial, the IGA is a lesion-specific assessment and will be evaluated separately for each target lesion.
b) The disease activity and damage scores are based on the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) and the Revised CLASI (RCLASI) which are validated scoring systems to assess disease activity and damage in patients with cutaneous lupus erythematosus.
c) In this trial, the PaGA is a lesion-specific assessment and will be evaluated separately for each target lesion.
Abbreviations: AE = adverse event; DLE = discoid lupus erythematosus; IMP = investigational medicinal product.

7 Trial design

7.1 Overall trial design

Overview

This is a phase 2a, multi-centre, double-blind, randomised, within-subject, vehicle-controlled trial. The trial will investigate the efficacy and safety of delgocitinib cream 20 mg/g in adult subjects with DLE after 6 weeks of treatment. The trial design is illustrated in Section 3.

Each subject must have at least 2 DLE target lesions with active disease (referred to as lesion 1 and 2) fulfilling the inclusion criteria (Section 8.2). The 2 target lesions will be randomised 1:1 to active and vehicle treatment.

The different trial periods and the visit structure are further described below. An overview of the scheduled trial procedures is shown in Section 4.

Screening period (Day -28 to Day -7)

A screening visit will take place 7 to 28 days prior to the first application of IMP.

Before any trial-related procedures are started, the subjects will receive the necessary written and verbal information and instructions and sign the informed consent form(s). Each subject will receive a unique subject identification number (subject ID), and eligibility will be assessed by investigator assessments, clinical laboratory tests, and ECG.

Treatment period (Day 1 to Week 6)

At baseline (Day 1), the subjects' eligibility to enter the trial will be confirmed by re-checking the eligibility criteria and evaluating the laboratory results for the samples taken at the screening visit. The investigator must ensure that laboratory results which are needed to assess eligibility have been received and reviewed. All eligible subjects will continue in the trial. The 2 target lesions will be randomly assigned (1:1) to treatment with delgocitinib cream 20 mg/g and vehicle. The randomised treatment will be applied to each lesion twice daily for 6 weeks. The first application of the IMP will occur at the trial site on Day 1 when all baseline assessments have been carried out. The subsequent IMP applications will be performed by the subject at home.

During the 6-week treatment period, the subjects will return to the trial site for scheduled visits at Weeks 2, 4, and 6. The last application of IMP will occur the evening before the subjects attend the visit scheduled at Week 6. The efficacy and safety assessments during the

treatment period will be performed as described in Section 4. The primary endpoint is assessed at Week 6.

Safety follow-up period (Week 6 to Week 8)

All randomised subjects will attend a safety follow-up visit 2 weeks after the last application of IMP. This will mark the end of trial participation for subjects who have completed the entire trial. Subjects who discontinue IMP treatment or prematurely withdraw from the trial will be followed up as described in Section 10.

7.2 Number of subjects needed

This trial aims to have 36 subjects evaluable for the primary endpoint. Assuming a drop-out rate of 20%, approximately 45 subjects will be randomised to achieve this.

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

This trial will be conducted at approximately 20 sites in several countries in the EU and/or United States. There is no minimum or maximum number of subjects per trial site.

A subgroup of 20-30 subjects from selected countries is targeted for participation in the qualitative exit interviews (Section 11.6.1.3). This sample size is based on typical sample sizes required for qualitative exploration of patient experience concepts (24).

7.3 End of trial definition

Subjects will be considered to have completed the trial if they have completed all periods of the trial including the safety follow-up visit.

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

Final collection of data for the primary endpoint occurs at Week 6.

7.4 Software

Clinical Data Interchange Standards Consortium (CDISC) controlled terminology version 30-Mar-2018 was used for definition of controlled terminology used throughout this protocol and will be used for statistical programming and output. Study data tabulation model (SDTM) version 1.5 will be used for data tabulations.

8 Trial population

8.1 Subject eligibility

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

The subject's eligibility for the clinical trial must be verified according to the inclusion and exclusion criteria at visits specified in Section 4. It will be recorded in the eCRF if the subject has met all the inclusion criteria and none of the exclusion criteria.

Any implementation of national requirements/law for the subject's participation in the clinical trial will be ensured and described in submission documentation to regulatory authorities and institutional review boards (IRBs)/independent ethics committees (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 18-70 years.
3. Histopathological findings (current or previous) consistent with clinical diagnosis of DLE.
4. Unequivocal clinical diagnosis of 2 active DLE target lesions that are <6 months old and amenable for clinical evaluation. This includes lesions located on the scalp if they fulfil all lesion-specific eligibility criteria.
5. Target lesion IGA score of at least moderate severity (IGA ≥3) at screening and baseline.
6. Target lesion erythema score ≥2 at screening and baseline.
7. For subjects taking hydroxychloroquine or chloroquine: No abnormal findings at the latest routine ophthalmologic examination, and no routine ophthalmologic examination is planned during the trial.
8. Female subjects of childbearing potential* must use a highly effective** form of birth control throughout the trial and for at least 2 weeks after last administration of IMP.

* A female subject is defined as not being of childbearing potential if she is postmenopausal (at least 12 months with no menses without an alternative medical cause prior to screening), or surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

**A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year) such as bilateral tubal occlusion, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), sexual abstinence (when this is in line with the preferred and usual life style of the subject), vasectomised partner (given that the subject is monogamous).

9. Prospective ability to attend all scheduled trial visits.

8.3 Exclusion criteria

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

1. Target lesion dyspigmentation score of 2 at screening or baseline.
2. Target lesion scarring/atrophy score of 2 at screening or baseline.
3. Target lesion scarring alopecia score of >0 in scalp lesions at screening or baseline.
4. Medical history of SLE with clinically significant organ involvement (American College of Rheumatology SLE classification criteria no. 6 to 9, see Appendix 6) including SLE-related pleuritis or pericarditis (by clinical evaluation and electrocardiogram), and neurologic, renal, and/or other major SLE-related organ system involvement. SLE joint involvement is acceptable.
5. Subjects with unstable or significant SLE disease activity findings that would, by its progressive nature and/or severity, interfere with the trial evaluation, completion, and/or procedures per the investigator's discretion.
6. Other skin conditions at screening or baseline that would interfere with the evaluation of DLE.
7. Immunosuppressive/immunomodulating therapy with e.g. methotrexate, cyclosporine, azathioprine, retinoids (both topical and systemic), or dapsone within 4 weeks prior to baseline.

8. Systemic prednisolone >7.5 mg/day or changed dose within 4 weeks prior to baseline (nasal and inhaled corticosteroids are allowed).
9. Treatment with the following medications:
    - Oral antimalarial treatment with hydroxychloroquine >6.5 mg/kg body weight/day, or chloroquine >4 mg/kg body weight/day, or changed dose within 12 weeks prior to baseline.
    - Quinacrine combined with either hydroxychloroquine or chloroquine within 12 weeks prior to baseline.
    - Drugs known to interact with antimalarials (e.g. digoxin, cimetidine) within 12 weeks prior to baseline (only applicable to subjects taking antimalarial treatment).
10. Treatment with topical corticosteroids, calcineurin inhibitors, and phosphodiesterase-4 (PDE-4) inhibitors within 2 weeks prior to baseline.
11. Use of systemic antibiotics or cutaneously applied antibiotics on the target lesions within 2 weeks prior to baseline.
12. UV therapy or excessive sun exposure within 2 weeks prior to baseline.
13. Any procedure impairing the skin barrier (e.g. incision) within 2 cm from the border of any of the target lesions within 4 weeks prior to baseline.
14. Receipt of live (attenuated) vaccines within 4 weeks prior to baseline.
15. Treatment with any marketed biological therapy or investigational biologic agents:
    - 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 prior to baseline, whichever is longer.
16. Treatment with any non-marketed drug substance (that is, an agent which has not yet been made available for clinical use following registration) within 4 weeks or 5 half-lives prior to baseline, whichever is longer.
17. Unstable or fluctuating use of tobacco within 1 month prior to screening which, in the opinion of the investigator, may affect the natural course of the disease and thus affect the evaluation of the treatment.

18. History of any active skin infection within 1 week prior to baseline.
19. 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.
20. Tuberculosis requiring treatment within 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 at screening.
21. Immunosuppressed or immunocompromised subjects.
22. Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.
23. 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.
24. Any disorder which is not stable and could:
    - Affect the safety of the subject throughout the trial.
    - Influence the findings of the trial.
    - Impede the subject's ability to complete the trial.

Examples include but are not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, and psychiatric disorders, and major physical impairment.

25. Any abnormal finding which may:
    - Put the subject at risk because of their participation in the trial.
    - Influence the results of the trial.
    - Influence the subject's ability to complete the trial.

    The abnormal finding must be clinically significant and observed during the screening period. Examples include abnormal findings in physical examination, vital signs, ECG, haematology, clinical chemistry, or urinalysis.
26. Positive human immunodeficiency virus antibody, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV) serology at screening.
27. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2×upper limit of normal (ULN) and/or a serum creatinine level ≥1.5×ULN at screening.
28. Known or suspected hypersensitivity to any component(s) of the IMPs.
29. Current participation in any other interventional clinical trial.
30. Previous randomisation in this clinical trial.
31. Previous participated in a clinical trial with delgocitinib (LEO 124249).
32. 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.
33. Subjects who in the opinion of the investigator are likely to be non-compliant or unable to understand the trial and give adequately informed consent.
34. Employees of the trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.
35. Subjects who are legally institutionalised.
36. Female subjects who are 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 ID

will be assigned by a central interactive response technology (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 assigned to trial treatment. A minimal set of screening failure information is required to ensure transparent reporting of screening failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (25) and to respond to queries from regulatory authorities.

DLE is a rare disease, and the number of eligible patients is limited. Therefore, subjects who fail to meet all eligibility criteria at screening may be re-assessed for eligibility at a later stage at the investigator's discretion. This applies only to eligibility criteria that are likely to be fulfilled over time, e.g. criteria concerning DLE severity and prohibited medications. Re-assessment of eligibility will be allowed at the investigator's discretion if one or more of the following eligibility criteria are not fulfilled at screening:

- Inclusion criteria no. 5, 6, and 7.
- Exclusion criteria no. 6, 7, 8, 9, 13, 14, 15, 16, and 19.

If any other eligibility criteria are not fulfilled at screening, the subject will be considered a screening failure. However, if the reason for screening failure is administrative (e.g. delayed test results and not due to the subject failing to fulfil the eligibility criteria), re-assessment of eligibility may also be permitted. Each subject can only be re-assessed for eligibility once.

At screening, it will be clearly documented in the eCRF and in the source data if a subject is planned to return for re-assessment of eligibility. Subjects who fail to return for re-assessment

of eligibility will be considered screening failures. Each subject will keep the same subject ID during the trial.

If the period between screening and re-assessment of eligibility exceeds 4 weeks, all screening procedures including laboratory samples must be repeated at the re-assessment visit. In this case, the re-assessment of eligibility will be documented as a full, additional screening visit in the eCRF. For shorter periods (<4 weeks) between screening and re-assessment of eligibility, the investigator will judge which assessments and procedures are relevant at the re-assessment visit.

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

- Date of informed consent.
- Demographics (date of birth, sex, ethnicity, race). If full date of birth is not allowed to be recorded per local legislation, month and/or year of birth should be collected together with the subject's age.
- Reason for screening failure.
    - Failure to meet eligibility criteria.
    - Lost to follow-up.
    - Withdrawal by subject.
    - Other.
- Date of screening failure.
- Any adverse events (AEs) and serious AEs (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 investigational medicinal products

Investigational medicinal product	Dosage form	Active ingredient and concentration	Pack size	Source
Delgocitinib cream 20 mg/g.	Cream.	Delgocitinib 20 mg/g.	15 g.	CCI [redacted]
Delgocitinib cream vehicle.	Cream.	Vehicle.	15 g.	CCI [redacted]

9.2 Administration of IMP

The IMPs (delgocitinib cream and vehicle) will be administered as topical applications twice daily for 6 weeks. The 2 target lesions (referred to as lesion 1 and 2, see Section 11.2.8) will be randomised 1:1 to treatment with delgocitinib cream 20 mg/g or vehicle. The subjects will apply the IMPs in the morning and in the evening, approximately 12 hours apart. Instructions for use will be provided.

For each target lesion, the treatment area will be defined as the lesion area at baseline plus a margin of approximately 1 cm. The first application of the IMPs will occur on Day 1 at the trial site after all assessments have been completed. Prior to the first IMP application, the subjects will be instructed how much cream to apply and which IMP to use on each treatment area. The instructions will be given by trial site staff who are not involved in clinical assessments during the trial. The identification of the 2 target lesions and the allocation of treatment to each lesion is further described in Section 9.3.

The amount of IMP to be applied to each treatment area depends on the size of the target lesions. If a target lesion remains unchanged or decrease in size, the treatment area will remain constant during the treatment period even if the symptoms improve. If a target lesion increases in size, the treatment area will increase correspondingly. The IMPs should be applied in an even layer to cover the entire treatment area. The maximum expected treatment area is 1% of BSA corresponding to a lesion of 15 cm in diameter. For reference, it is estimated that 0.3 g of cream will be adequate to cover 1% of BSA (an area corresponding to the subject's hand; the palmar surface plus the 5 digits).

The subjects will continue treatment until visit 5 (Week 6) regardless of clearance status. The last application of the IMPs will occur at the subject's home the day before the subject attends the Week 6 visit.

The subjects should not shower within 2 hours after applying the IMPs. At the scheduled visits, investigator assessments and PaGA should be done prior to or at least 2 hours after IMP application and/or bathing/showering. Non-invasive skin sampling should be done prior to or at least 4 hours after IMP application. Note that on the day of the Week 6 visit, no IMP will be applied in the morning.

In addition to the IMPs, all subjects should apply sunscreen every day during the treatment period (Section 9.4). The sunscreen should be applied to sun-exposed areas in the morning, at least 45 minutes after application of IMP.

On the treatment areas, only the IMPs and sunscreen can be applied. On DLE lesions outside the treatment areas, only sunscreen and emollients are allowed (see also Section 9.7). This is to avoid confusing the subjects by having to apply more than 2 treatments, as accidental use of other medications on the treatment areas could impact both efficacy and safety assessments.

The IMPs will be dispensed at the visits shown in the schedule of trial procedures (Section 4).

LEO does not recommend specific treatment for an overdose. The investigator will use clinical judgement to treat any overdose if necessary (Section 13.6.2).

9.3 Treatment assignment

Subjects who have been found to comply with all the inclusion criteria and not to violate any of the exclusion criteria will be assigned to treatment at baseline (Day 1).

All subjects will receive the same 2 treatments (delgocitinib cream and vehicle), so there will be no subdivision into treatment groups. At screening, 2 potential target lesions are selected and evaluated. At baseline, the potential target lesions are re-evaluated. In the unlikely event that 1 or both of the potential target lesions selected at screening no longer fulfil all the eligibility criteria at baseline, the investigator is allowed to select new, eligible target lesions (if available) at baseline, as long as this is clearly documented in the source data and the eCRF (see Section 11.2.8).

After confirmation of eligibility at baseline, the selected target lesions will be numbered as lesion 1 and 2. The numbering should begin with the uppermost or most proximal site on the left from the investigator's view. Lesions along the same line should be numbered from left to right.

Randomisation will be performed by permutation of the treatment codes A and B. Each subject will be randomly assigned to either the treatment sequence AB or the treatment sequence BA with the probability 0.5. The first treatment listed in the treatment sequence will be assigned to lesion 1 and the last treatment will be assigned to lesion 2.

The IRT system will assign the required kit number for each subject and will also be used for IMP supply chain and expiry tracking.

9.3.1 Blinding

The packaging and labelling of the IMPs will contain no evidence of their identity. However, there is a slight difference in colour between the 2 IMPs. The difference is only discernible on close inspection with both IMPs compared side by side. To avoid accidental investigator unblinding, the first application of IMPs and instructions to the subjects will only be done by designated trial site staff who are not involved in clinical evaluations.

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

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

9.4 Background treatment

All subjects will be instructed to apply sunscreen daily to sun-exposed areas during the treatment period. The sunscreen must have a sun protection factor (SPF) of at least 50 and will be provided to all subjects by the trial site. If the subject is known to be hypersensitive to the provided sunscreen or has a strong preference for a particular brand, the subject can be allowed to use his/her preferred sunscreen with SPF of at least 50. The sunscreen should be applied in the morning, at least 45 minutes after application of IMP.

9.5 Rescue treatment

Not applicable.

9.6 Concomitant medication and concurrent procedures

Current medication or vaccines from baseline through safety follow-up as well as medication listed as prohibited medication in the exclusion criteria that the subject receives from 6 months prior to baseline must be recorded (if relevant) 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 also be recorded if the treatment is within 5 cm of a target lesion (and if so, which of the target lesions).

Any concurrent procedure from baseline through safety follow-up as well as procedures listed as prohibited procedures in the exclusion criteria from 4 weeks prior to baseline 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 cutaneous procedures, it must also be recorded if the procedure is inside a target lesion (and if so, which of the target lesions).

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

If analgesic treatment is considered necessary during the trial, the following concomitant medications are recommended and allowed from screening through safety follow-up:

- For subjects with mild SLE: ibuprofen ≤1200 mg/day (or equivalents in their corresponding recommended maximum daily dose), provided that this is known to be well tolerated by the subject.
- For subjects without SLE: paracetamol ≤4000 mg/day should be used instead of ibuprofen.

9.7 Prohibited medication and procedures

The medications listed in Panel 5 are prohibited during the trial. Note that some medications are prohibited prior to screening and/or randomisation, but allowed during the treatment phase (see the exclusion criteria, Section 8.3). Note that any changes in dose or discontinuation of medications or procedures that are listed as prohibited prior to or during the trial should only be done for medical reasons, not trial-related reasons.

Panel 5: Prohibited medication and procedures

Medication/procedure	Prohibited from	Prohibited to
Systemic prednisolone >7.5 mg/day or changed dose (nasal and inhaled corticosteroids allowed).	4 weeks prior to baseline.	End of trial.
Oral antimalarial treatment with hydroxychloroquine >6.5 mg/kg/day or chloroquine >4 mg/kg/day, or changed dose.	12 weeks prior to baseline.	End of trial.
Quinacrine combined with either hydroxychloroquine or chloroquine.	12 weeks prior to baseline.	End of trial.
Drugs known to interact with antimalarials (e.g. digoxin, cimetidine)[a].	12 weeks prior to baseline.	End of trial.
Immunosuppressive/immunomodulating therapy with e.g. methotrexate, cyclosporine, azathioprine, retinoids (both topical and systemic), or dapsone.	4 weeks prior to baseline.	End of trial.
Biologics (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 prior to baseline, whichever is longer.	End of trial.
Topical corticosteroids, calcineurin inhibitors, and PDE-4 inhibitors.	2 weeks prior to baseline.	End of trial.
Any cutaneously applied product (other than sunscreen and IMPs) on the treatment areas.	Randomisation.	End of trial.
Any cutaneously applied product (other than sunscreen and emollients) on DLE lesions outside the treatment areas.	Randomisation.	End of trial.
Cutaneously applied antibiotics on the treatment areas.	2 weeks prior to baseline.	End of trial.
UV therapy or excessive sun exposure.	2 weeks prior to baseline.	End of trial.
Live (attenuated) vaccine.	4 weeks 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 or 5 half-lives prior to baseline, whichever is longer.	End of trial.
Any procedure impairing the skin barrier (e.g. incision) within 2 cm from the border of any of the target lesions.	4 weeks prior to baseline.	End of trial.

a) Only applicable to subjects taking antimalarial treatment.

Abbreviations: DLE = discoid lupus erythematosus; IMP = investigational medicinal product; PDE-4 = phosphodiesterase; UV = ultraviolet.

In case any prohibited treatments are used during the trial, they must be recorded as concomitant medication.

Normal bathing and washing is allowed following the subject's normal routine but should be done at least 2 hours after application of the IMPs.

Use of cosmetic body care products (e.g. make-up, body lotion, bath oil) and emollients is not allowed on the target lesions from baseline to safety follow-up.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

Investigational medicinal products

The IMPs will be packaged in individually numbered kits. Primary and secondary packaging materials will be individually labelled. The 2 IMPs (treatment A and B) will have labels in different colours to help the subjects distinguish between them.

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 IMPs must be stored at 2-8°C at the trial site and at the subject's home. Do not freeze. At the trial site, the storage temperature must be monitored as described below depending on the temperature recording system:

- For electronic, continuously recording systems with alarm and back-up of data: If no alarm is triggered, a log must be printed, reviewed, signed, and dated each month.
- For electronic, continuously recording systems with alarm and no back-up of data: If no alarm is triggered, a manual handwritten log is maintained and should be reviewed, signed, and dated each week. In addition, a log must be printed, reviewed, signed, and dated each month.

If the alarm is triggered (regardless of system type), 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 to document the storage within the right temperature interval. Storage facilities should be checked at least every working day.

Storage of 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 clinical research associate (CRA) for further guidance:

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

Damaged IMPs should be documented in the IRT system and reported as a product complaint to Global Safety, LEO (see Section 9.10). Damaged IMPs 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 damaged kits) 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 IMPs 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 IMPs. Drug accountability information will be entered in the IRT system, where also inventory status of all IMPs at the trial site will be maintained.

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

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

All IMPs (including packaging material) supplied by the contract manufacturing organisation (CMO) on behalf of LEO will be returned to the CMO on an ongoing basis. Prior to their return, the IMPs must be fully accounted for by the CRA with the help of site staff responsible for dispensing the IMPs. Accountability must be documented on drug accountability forms.

All tubes returned to the CMO will be weighed to determine the amount of IMP used by each subject. The average weight of a full, labelled tube will be provided by the CMO.

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 IMPs will occur at the trial site with clear instructions from the site staff on which IMP to use on each target lesion and how much IMP to use per application (see Section 9.2).

At the visits specified in the schedule of trial procedures (Section 4), the subject will be asked if they have used the IMPs as prescribed. If a subject is found to be non-compliant, the investigator should remind the subject of the importance of following the instructions given, including applying the IMPs as prescribed. It must be recorded in the eCRF whether the subject is compliant or non-compliant. For non-compliant subjects, the reason for non-compliance and the nature of non-compliance (i.e. the number of missed or excessive applications of IMP, or use of the wrong IMP on 1 or both target lesions) will also be recorded.

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

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 IMPs (e.g. strange colour or consistency, inadequate labelling) must be reported to Global Safety 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. an SAE)) must be reported to Global Safety, 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 IMPs 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 system.

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

Global Safety, LEO contact information for reporting product complaints:

Fax number: +45 7226 3287

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

10 Discontinuation and withdrawal

10.1 General principles

A subject may withdraw from the trial (i.e. withdraw from treatment and any protocol-defined interventions) or permanently discontinue trial treatment (i.e. stop trial treatment only, but agree to continued protocol-defined interventions) at any time (prior to first application 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 discontinue IMP or withdraw from the trial will not be replaced.

Data to be recorded in the eCRF

The primary reasons for withdrawal from the trial, discontinuation of IMP, and not attending the primary endpoint visit (if applicable) 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.
- Death.
- Pregnancy.
- 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 permanently discontinue IMP in the event of:

- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing. This includes unacceptable worsening of DLE symptoms.
- Evidence of pregnancy.
- Clinically important laboratory abnormalities:
    - ALT and/or AST values >3×ULN with total bilirubin >2×ULN (unless elevated bilirubin is related to Gilbert-Meulengracht syndrome).
    - Confirmed ALT and/or AST >5×ULN.

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, primary endpoint visit, or the safety follow-up visit, whichever comes last).

Withdrawal from trial

Subjects who withdraw from the trial for any reason should attend an early termination visit as soon as possible after last administration of IMP (see 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 6 will be asked to attend an early termination visit as soon as possible after last administration of IMP and return to the trial site for 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 6 will be asked to attend:

- Early termination visit.
- Primary endpoint visit (Week 6).
- Safety follow-up visit (2 weeks after last administration of IMP).

The trial site will be allowed to schedule the primary endpoint visit and the safety follow-up visit on the same day if this complies with the visit windows for both visits.

10.4 Lost to follow-up

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

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

- The trial site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject. 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

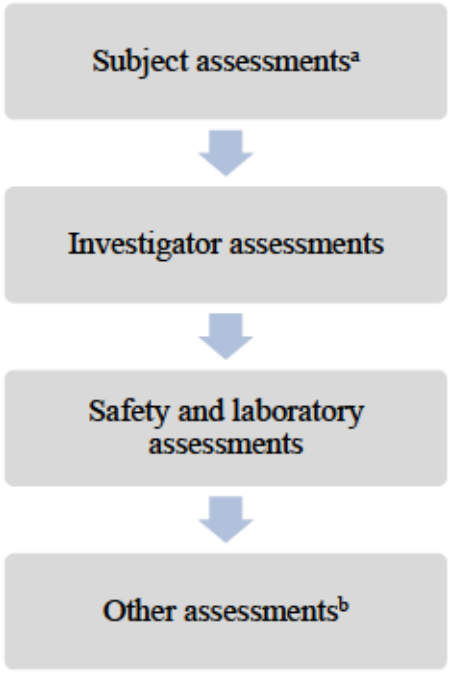
11.1 Overview

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.

The subject and investigator assessments must be done prior to or at least 2 hours after application of IMP or bathing/showering to ensure reliable evaluation of the target lesion (see Section 9.2). Non-invasive skin sampling should be done prior to or at least 4 hours after IMP application.

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

Panel 6: Sequence of assessments



a) At the screening visit, the subject's eligibility to enter the trial must be confirmed before any subject assessments can be completed.
b) Photographs of lesions (optional), non-invasive skin sampling, skin biopsies (optional).

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

required by the protocol. In United States, the investigator can also be a certified physician's assistant or advanced registered nurse practitioner.

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

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

The investigator(s) performing the assessments must not be involved in the administration of IMPs (see Section 9.3.1).

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 per local legislation, month and/or 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 subject): 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:

- DLE-relevant history:
    - Age of onset of DLE.
    - Previous DLE treatments.
    - Other autoimmune diseases.
    - LE-nonspecific lesions.
    - Sunscreen use.
    - History of smoking.
    - History of photosensitivity.
- Skin disease history: all past and current skin disease history should be collected; for each diagnosis, the start date and stop date will be recorded (it will also be recorded if the diagnosis is ongoing). It will be recorded if the disease is/has been present inside or within 2 cm of the border of any of the target lesions (this information will be entered into the eCRF at baseline when the 2 selected target lesions have been confirmed as eligible).

- Other medical and surgical history including concurrent diagnoses within the previous 12 months. For each condition, diagnosis, or surgical procedure, the start date and stop date will be recorded. It will also be recorded if the condition, diagnosis, or surgical procedure is ongoing and if it is/has been present in any of the target lesions.

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

11.2.4 Height and weight

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

11.2.5 Classification of systemic lupus erythematosus

The most widely used classification criteria for SLE are those developed by the American College of Rheumatology (ACR) (revised in 1997, see Appendix 6) (26). The patient is classified with SLE using the ACR criteria if 4 or more of the manifestations are present, either serially or simultaneously, during any interval of observations. The investigator will score the different criteria to determine classification of SLE for each subject based on medical history, physical examination (Section 11.4.2), and lab samples (Section 11.4.4). See Panel 8 for scoring instructions.

Panel 8: Scoring instructions for the American College of Rheumatology criteria for classification of systemic lupus erythematosus

Criterion	Item	Source	Score
1	Malar rash.	Medical history, physical examination.	Yes = 1 No = 0
2	Discoid rash.	Medical history, physical examination.	Yes = 1 No = 0
3	Photosensitivity.	Medical history, physical examination.	Yes = 1 No = 0
4	Oral ulcers.	Medical history, physical examination.	Yes = 1 No = 0
5	Non-erosive arthritis.	Medical history, physical examination.	Yes = 1 No = 0
6	Pleuritis or pericarditis.	Medical history, physical examination, electrocardiogram.	Yes = 1 No = 0 If Yes, subject is not eligible.
7	Renal disorder.	Urinalysis.	Yes = 1 No = 0 If Yes, subject is not eligible.
8	Neurologic disorder.	Medical history, physical examination.	Yes = 1 No = 0 If Yes, subject is not eligible.
9	Haematologic disorder.	Blood sample.	Yes = 1 No = 0 If Yes, subject is not eligible.
10	Immunologic disorder.	Blood sample.	Yes = 1 No = 0
11	Positive antinuclear antibody.	Blood sample.	Yes = 1 No = 0

All scores of the individual criteria must be reported in the eCRF as well as the total score. For eligible subjects, the score for criteria no. 6 to 9 will be 0.

Any abnormal test results found as part of the classification of SLE will be followed up at the discretion of the investigator.

11.2.6 Cutaneous Lupus Erythematosus Disease Area and Severity Index

The CLASI is a validated scoring system to assess disease activity and damage in patients with CLE, taking both anatomical region and morphological aspects into account (27) (Appendix 7). Activity is scored based on erythema, scale/hypertrophy, mucous membrane lesions, and alopecia. Damage is scored in terms of dyspigmentation,

scarring/atrophy/panniculitis, and scarring of the scalp. The CLASI score is the sum of the total activity and damage scores which are calculated by simple addition of the subtotals. A high CLASI score indicates more severe disease.

At screening, the subjects will be scored according to the CLASI and its revised version RCLASI for a global disease assessment. See Section 11.2.7 for collection in the eCRF.

11.2.7 Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index

The RCLASI is a revised, validated version of the CLASI (see Section 11.2.6). As the CLASI, the RCLASI is a tool to assess disease activity and damage in patients with CLE, taking both anatomical region and morphological aspects into account (Appendix 8) (28). In addition to erythema and scaling/hyperkeratosis, the RCLASI scores disease activity by oedema/infiltration and subcutaneous nodules/plaques. Mucous membrane lesions, non-scarring alopecia, and 'lupus hair' are also scored. Damage is scored in terms of dyspigmentation, scarring/atrophy, and scarring alopecia. The RCLASI score is the sum of the total activity and damage scores which are calculated by simple addition of the subtotals. A high RCLASI score indicates more severe disease.

At screening, the subjects will be scored according to the CLASI and RCLASI for a global disease assessment. The investigator will score all the elements according to the eCRF. To ease data collection, overlapping elements will only be recorded once.

At all subsequent scheduled visits, only the elements concerning skin lesion activity and damage will be assessed for each of the target lesions (see Sections 11.3.2 and 11.3.3).

11.2.8 Identification of target lesions

The investigator will identify 2 comparable DLE lesions which are less than 6 months old and have clinical signs of disease activity according to the eligibility criteria. There is no lower limit for size of the target lesions as long as they are considered large enough for complete clinical evaluation. The maximum expected lesion size is 15 cm in diameter corresponding to 1% of BSA (1). The size of each target lesion will also be recorded (see Section 11.6.2).

The 2 target lesions should preferably be located in the same anatomical region, but priority should be given to the similarity in clinical appearance of disease activity signs. If there are more than 2 lesions amenable for clinical evaluation, the investigator will select the 2 lesions which are most suitable as target lesions. Lesions on the scalp may also be included if they fulfil the eligibility criteria.

The investigator will identify and evaluate 2 potential target lesions at screening and will assess these again at baseline to make sure that both target lesions meet the necessary requirements. In the unlikely event that a potential target lesion selected at screening no longer meets all eligibility criteria at baseline, the investigator has the option to select a new target lesion, if available. It will be documented in the source data and the eCRF whether the target lesions selected for randomisation at baseline are the same as the potential target lesions identified at screening (see also Section 9.3).

At baseline, the selected target lesions will be numbered (lesion 1 and 2) as described in Section 9.3, and the location of the target lesions will be recorded in the eCRF (scalp, forehead, temple, malar, cheek, eyebrow, lower eyelid, upper eyelid, lower lip, upper lip, chin, external ear, external nose, neck, trunk, arm, or leg). The location of the lesions will be specified in more detail in the subject records to ensure correct identification of the lesions at subsequent visits.

11.3 Efficacy assessments

11.3.1 Investigator's Global Assessment

The IGA is an instrument used in clinical trials to rate the severity of the subject's global disease and is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Panel 9). In this trial, the investigator will use the IGA as a lesion-specific assessment to rate the severity of DLE for each of the 2 target lesions.

The IGA 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 <u>not</u> in relation to the condition at a previous visit.

Panel 9: Investigator's Global Assessment for discoid lupus erythematosus

Score	Disease severity	Morphological description
0	Clear.	No activity signs of DLE (no erythema, no scaling/hyperkeratosis, no oedema/infiltration). Damage signs may be present (dyspigmentation and/or scarring/atrophy).
1	Almost clear.	Pink or faint erythema only. No scaling/hyperkeratosis, no oedema/infiltration.
2	Mild.	Pink or faint erythema. Slight scaling (mostly fine scales) and/or slight dermal oedema.
3	Moderate.	Prominent erythema. Slight scaling (mostly fine to circumscribed adherent scales) and/or slight to definite dermal oedema.
4	Severe.	Prominent red, dark red, purple, or violaceous colour. Crusting may be present. Severe scaling with follicular plugging and/or dermal oedema with skin induration.

Abbreviation: DLE = discoid lupus erythematosus.

11.3.2 Skin lesion activity

The assessment of skin lesion activity and skin lesion damage (Section 11.3.3) are based on the CLASI and RCLASI scoring scales for relevant disease signs (see Sections 11.2.6 and 11.2.7). The investigator will assess each target lesion for skin lesion activity at the visits indicated in the schedule of trial procedures (Section 4). The total skin disease activity score is defined as the sum of scores for erythema, scaling/hyperkeratosis, and oedema/infiltration.

Erythema

The investigator will score erythema for each target lesion on a 4-point scale:

0 = Absent.
1 = Pink, faint.
2 = Red.
3 = Dark red, purple/violaceous/crusted/haemorrhagic.

Scaling/hyperkeratosis

The investigator will give a combined score for scaling and hyperkeratosis for each target lesion on a 3-point scale:

0 = Absent.
1 = Circumscribed adherent scaling/follicular plugging.
2 = Verrucous hyperkeratosis.

Oedema/infiltration

The investigator will give a combined score for oedema and infiltration for each target lesion on a 3-point scale:

0 = Absent.
1 = Slight, just palpable.
2 = Palpable and visible.

11.3.3 Skin lesion damage

The assessment of skin lesion activity (Section 11.3.2) and skin lesion damage are based on the CLASI and RCLASI scoring scales for relevant disease signs. The investigator will assess each target lesion for skin lesion damage at the visits indicated in the schedule of trial procedures (Section 4). The total skin disease damage score is defined as the sum of scores for dyspigmentation and scarring/atrophy.

Dyspigmentation

The investigator will score dyspigmentation for each target lesion on a 4-point scale:

0 = Absent.
1a = Hypopigmentation.
1b = Hyperpigmentation.
2 = Hypo- and hyperpigmentation.

Scarring/atrophy

The investigator will give a combined score for scarring and atrophy for each target lesion on a 3-point scale:

0 = Absent.
1 = Initial scarring.
2 = Severe firm/atrophic/vermicular scarring.

11.4 Safety assessments

11.4.1 Vital signs

Vital signs (resting blood pressure, peripheral pulse, and body temperature) must 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 clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be randomised into the trial.

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 and the date and time they were measured will be recorded in the eCRF. If vital signs were not measured, a reason should be given. 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 general physical examination of the subject must be performed according to the schedule of trial procedures (Section 4). This includes dermatologic examination of the skin, palpation of the abdominal organs, auscultation of heart, lungs, and abdomen, basic neurological status, and general examination of the eyes, ears, nose, and throat.

If an abnormal physical finding at screening is considered clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be randomised into the trial.

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

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

A preliminary evaluation of the ECGs will be performed by the investigator 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. 25).

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.

11.4.4 Laboratory testing

11.4.4.1 Overview

Blood and urine samples will be collected according to the schedule of trial procedures (Section 4).

The evaluations shown in Panel 10 will be performed.

Panel 10: 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 Haemoglobin A1c Albumin 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 Reticulocytes
Urinalysis[b]	**Serology[c]**
Appearance Bilirubin Blood[d] Colour Glucose Ketones Leukocyte esterase[d] Nitrite[d] Protein[d] Specific gravity Urobilinogen pH	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 Antinuclear antibody Anti-DNA Anti-Smith antibody Immunoglobulin G anticardiolipin antibody Immunoglobulin M anticardiolipin antibody Lupus anticoagulant Interferon gamma release test[f]
Urine pregnancy test[e]	
Human chorionic gonadotropin	

a) If bilirubin is above ULN, direct and indirect bilirubin will also be measured.
b) At screening, the urine sample will also be tested at the trial site with a urine dipstick to assess SLE-related renal disorder (see Section 11.2.5 and 11.4.4.2).
c) Measured at screening only.
d) In case of values outside the reference ranges, microscopic analysis will be performed.
e) Only female subjects of childbearing potential. The urine pregnancy test will have a minimum sensitivity of 25 mIU/mL.
f) Only subjects with high risk of latent tuberculosis.

Abbreviations: HDL = high density lipoprotein; HIV = human immunodeficiency virus; LDL = low density lipoprotein; ULN = upper limit of normal.

11.4.4.2 Investigator evaluation of laboratory samples

Central laboratory
Chemistry, haematology, urinalysis, and serology will be done 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 may be repeated if deemed relevant by the investigator.

If a screening laboratory result is abnormal and clinically significant, it will be at the investigator's discretion to decide if the subject should be randomised into the trial.

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
Female subjects of childbearing potential will have a urine pregnancy test performed at the trial site at screening and at baseline prior to randomisation. The test will be repeated at the visits shown in the schedule of trial procedures (Section 4). The date and the outcome of the urine pregnancy test will be recorded in the eCRF ('positive', 'negative').

At screening, the urine samples will be tested for proteinuria with a urine dipstick to assess SLE-related renal disorder (ACR criterion no. 7, see Section 11.2.5 and Appendix 6). If the test is positive for proteinuria, the urine dipstick test must be repeated at least 1 week after the first test. If the second test is also positive, the subject is considered a screening failure due to violation of exclusion criterion no. 4. If the second urine dipstick test is negative, the subject can be included in the trial, as the observed proteinuria is then considered transient and not a sign of renal disorder as such.

Reporting in eCRF
At each visit, the site staff will record in the eCRF if a sample was taken and, if applicable, the date as well as the investigator's assessment of the results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant'). If a sample was not taken, a reason will be provided.

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.

11.5 Pharmacodynamics and biomarkers

11.5.1 Overview

The pathogenesis of DLE is characterised by an inflammatory infiltrate localised in the dermis with presence of plasmacytoid dendritic cells and T cells. At the molecular level, the inflammatory response is dominated by type I and type II interferons and the chemokines CXCL9, CXCL10, and CXCL11, which are hallmarks of Th1 responses.

As an exploratory component of this trial, non-invasive skin samples and skin biopsies will be collected to create a general molecular profile of DLE and investigate how this profile changes upon treatment with delgocitinib. By comparing the expression of relevant biomarkers at the skin surface level (where drug exposure will be high) with changes across the whole skin depth in biopsies, it will be estimated to which extent the drug exposure in the dermis has been able to inhibit the pathogenic processes.

At all visits from baseline until end of treatment, non-invasive skin samples will be taken by applying a patch to the skin surface to absorb soluble material from the skin (see Section 11.5.2). After the trial, these patches will be analysed for disease-relevant cytokines and chemokines at the protein level. If no clinically relevant response to delgocitinib is seen, only patches from the baseline and end of treatment visits will be analysed.

Skin biopsies will be obtained at the end of treatment visit (Week 6) to analyse differences in gene expression (Section 11.5.3). Due to the invasive nature of this procedure, biopsies will be optional for the subjects. A focused panel of inflammatory and disease-related genes will be analysed by quantitative polymerase chain reaction (qPCR). A general expression analysis by microarray will be performed only if a clinically relevant response to delgocitinib is seen and if a sufficient number of biopsies is obtained to do a meaningful analysis.

Collection, handling, and shipment instructions for skin samples are provided in a separate laboratory manual. For subjects who do not complete the trial, the biopsies and non-invasive skin samples listed for Week 6 should be taken at the early termination visit.

A summary of the results will be included in the clinical trial report (CTR) if available at this time. The full results from the pharmacodynamics/biomarker analysis of all skin samples will be described separately in an addendum to the CTR.

11.5.2 Non-invasive skin sampling

Non-invasive sampling of the skin will be done by applying a small patch to the selected skin area for 15 minutes. This will allow the patch to absorb soluble proteins that can diffuse through the skin. The patch will then be stored frozen in a vial until it will be analysed after the trial. Non-invasive skin sampling will not be done for subjects who have plaster or bandage allergy.

At baseline (prior to the first application of IMPs) and at the visits indicated in the schedule of trial procedures (Section 4), patches will be applied to each of the 2 target lesions. A representative area of each lesion should be selected. Another patch will be applied to a non-lesional skin location of similar anatomical origin. This procedure must be done prior to or at least 4 hours after IMP application.

It will be recorded in the eCRF if the samples were taken; if not, a comment should be provided. The non-lesional locations will be documented in the eCRF (scalp, forehead, temple, malar, cheek, eyebrow, lower eyelid, upper eyelid, lower lip, upper lip, chin, external ear, external nose, neck, trunk, arm, or leg).

11.5.3 Skin biopsies (optional)

Subjects will be asked to provide skin biopsies. Participation in this component of the trial is optional and requires that the subject provides additional informed consent. Biopsies will not be taken if the investigator considers the procedure unsuitable for the subject (e.g. subjects receiving anticoagulant therapy).

3 skin punch biopsies (2 mm) for gene expression analysis will be taken at Week 6 or the early termination visit as specified in the schedule of trial procedures (Section 4). In case of an early termination visit, biopsies will only be taken if the subject has received treatment with the IMPs at least until the Week 2 visit.

Biopsies will be taken from each of the target lesions, and 1 biopsy will be taken from a non-lesional skin location of similar anatomical origin (same location used for non-invasive skin sampling at Week 6, see Section 11.5.2). Within each target lesion, the biopsy should be taken from a representative area of the lesion. For subjects who consent to having photographs taken, each target lesion should be photographed both before and after the biopsy to document the biopsy site.

The biopsies will be stored in tubes containing RNAlater at ambient temperature until the next day and then stored frozen until analysis.

For subjects who have provided consent to this part, it will be recorded in the eCRF if the biopsies were taken; if not, a comment should be provided. The non-lesional biopsy site will be documented in the eCRF.

A check of skin biopsy wound healing including removal of suture, if applicable, will be performed at the safety follow-up visit.

11.6 Other assessments

11.6.1 Subject assessments

11.6.1.1 Patient's Global Assessment

Subjects will assess the disease severity of each target lesion using the PaGA at the visits specified in the schedule of trial procedures (Section 4). The assessment will be made using the 5-point scale:

0 = Clear.
1 = Almost clear.
2 = Mild.
3 = Moderate.
4 = Severe.

The assessment will be based on the severity of the DLE lesions at the time of the assessment (and not in relation to the severity at previous visits). The PaGA should be completed before the investigator's assessments and without the investigator or site staff discussing the severity of the target lesions with the subject. The investigator will explain the categories of the scale to the subject who will then indicate which category should be ticked.

11.6.1.2 Dermatology Life Quality Index

The 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 such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment (29). 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 (Section 4).

11.6.1.3 Exit interviews (optional, selected countries only)

Qualitative, semi-structured exit interviews will be conducted with a subgroup of 20-30 subjects by experienced qualitative interviewers after the end of the treatment period (i.e. after Week 6 or early termination). The exit interviews will only be conducted in selected countries to reduce the number of languages.

The exit interviews will be conducted by telephone, in the subject's native language, at a date and time agreed with the subject at the Week 6 visit. The interviews will be scheduled to occur as soon as possible after Week 6 and within a maximum of 2 weeks. The participants will be the first 20-30 subjects who agree to take part in the exit interviews. Up to 8 of the interview participants can be subjects who withdraw from the trial prior to Week 6. These subjects will be interviewed within 2 weeks after their withdrawal from the trial.

Efforts will be made to ensure that the subgroup is representative of the general patient population with regards to age, sex, and baseline DLE severity.

Each interview is expected to last approximately 60 minutes. A semi-structured interview guide will be used to explore the lived experience of DLE from the patient perspective including signs/symptoms and their impact on domains of HRQoL. The findings from this part may be used to inform the selection, development, or modification of patient-reported outcomes and other endpoints for use in future DLE trials. Subjects will be asked about their experience of signs/symptoms and the impact on HRQoL domains, and any changes in those concepts prior to, during, and following participation in the trial. The interviews will also include questions aiming to understand the subjects' experience with the IMP and with trial procedures. Subjects who withdraw from the trial prior to Week 6 will also be asked about the reason for leaving the trial.

Interviewers will use the semi-structured interview guide to guide the discussion, and the interviews will be audio-recorded and transcribed verbatim for the purpose of accurate analysis. Qualitative analysis of the verbatim transcripts (translated into English) will be performed using thematic analysis. The analysis of the exit interview data will be reported separately as an addendum to the CTR. The interviewers will be trained in potential AE reporting and will report any potential AEs as per trial reporting procedures (Section 13.2).

11.6.2 Size of target lesions

The size of each target lesion will be assessed at the visits indicated in Section 4 and recorded in the eCRF. The longest diameter will be measured in cm (or inches) together with the

diameter perpendicular to this. The area will be calculated in cm^2 (or in^2). The target lesion area will be estimated by multiplying these 2 dimensions (i.e. longest diameter × perpendicular diameter).

11.6.3 Photography (optional)

Subjects will be asked to participate in a photography component involving digital photography for documentation. Participation in this photography component is optional and requires that the subject provides additional informed consent.

Digital colour photographs will be taken of each target lesion according to the schedule of trial procedures (Section 4). At Week 6, photographs should preferably be taken both before and after taking the biopsy (see Section 11.5.3).

For subjects who have provided consent to this part, it will be recorded in the eCRF if the photographs were taken; if not, a comment should be provided.

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

The photographs will have no other subject identifier than the subject ID and will be uploaded electronically to the eCRF under the relevant trial visit.

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 Estimate of total blood volume collected

Blood samples will be drawn for haematology, biochemistry, and serology. The total volume of blood to be drawn is less than 100 mL which is much less than the volume of blood drawn during a blood donation (500 mL).

11.8 End of trial

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

- Whether the subject completed the trial.
- Date of trial completion or discontinuation.
- Date and time of last administration of IMPs.
- Last scheduled visit number for which data is recorded.
- If applicable, primary reasons for discontinuation from IMP, withdrawal from trial, and not attending the primary endpoint visit (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 (that is, the early termination visit, the safety follow-up visit, or the primary endpoint visit, whichever comes last).

11.9 Storage of biological samples

Blood and urine safety laboratory samples will not be stored after the safety laboratory analysis is completed. Skin biopsies and non-invasive skin samples (patches) 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 of skin biopsies 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 the remaining material from the skin biopsies 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

12.1 Scientific rationale for trial design

This is a multi-centre, within-subject, randomised, vehicle-controlled, double-blind trial which will be conducted in accordance with the protocol, ICH-GCP, and applicable regulatory requirements. The primary objective is to demonstrate efficacy of delgocitinib cream 20 mg/g in DLE.

A double-blind design is chosen to prevent any bias from both subject and investigator. The randomisation will minimise selection bias and is considered the most reliable and impartial method of determining differences between treatments. Since this is the first trial with delgocitinib cream in DLE subjects, the cream vehicle will serve as reference to establish the efficacy and safety of delgocitinib.

The within-subject trial design is chosen because it allows direct comparison of delgocitinib cream and vehicle regarding signs of DLE with each subject being their own control which eliminates between-subject variation. This minimises the number of subjects needed which is a great advantage in a rare disease with a scarce patient population. CCI [redacted]

The trial population is selected to be homogeneous to reduce the biological variation and thereby reduce the number of subjects needed to evaluate the efficacy of delgocitinib. The eligibility criteria are designed to minimise any risk associated with trial participation (e.g. exclusion of SLE patients with major organ involvement).

Topical application is considered the preferred route of administration for treatments of DLE, since this is a cutaneous disease most often characterised by few lesions affecting small areas of the skin. CCI [redacted]

CCI [redacted]. Based on these considerations, treatment of DLE patients with delgocitinib cream 20 mg/g twice daily (on a BSA of approximately 1%) is expected to be safe and well tolerated.

12.2 Appropriateness of assessments

The trial endpoints have been selected to evaluate the efficacy of delgocitinib in reducing the disease activity of DLE. The clinical efficacy of delgocitinib will be assessed using the IGA and specific disease activity scores from the CLASI and RCLASI.

There is no single, standardised grading system for disease severity in DLE. The IGA scale is a static, ordinal, 5-point scale used to rate the subjects' disease from 'clear' to 'severe' (see Section 11.3.1). The scale is defined by distinct and clinically relevant morphological descriptions to minimise inter-rater variation.

The 2 target lesions will be evaluated and scored separately. The IGA scale will allow for an overall qualitative assessment of the disease severity of the target lesions. The scale can be dichotomised to treatment success (score 0 or 1 at Week 6, that is, a ≥2-point reduction in IGA score from baseline) and failure, representing a meaningful clinical outcome.

The CLASI and RCLASI have been developed and validated for assessment of disease severity in CLE patients. Both the CLASI and RCLASI score the activity and damage of the disease separately, considering both anatomical region and morphological aspects of skin lesions. In this trial, the skin lesion activity and damage signs scores are applied to the target lesions only. The individual sign scores and sum will give a quantitative assessment of the treatment effect. In addition, full CLASI and RCLASI assessments will be done at screening to describe the overall CLE disease burden in the trial population.

The PaGA is included to capture the subjects' perception of disease severity.

The safety of the IMP will be assessed by vital signs and clinical laboratory measurements and AE monitoring which will include local tolerability.

Skin biopsies (optional) and non-invasive skin samples will be taken for analysis of expression of inflammatory and disease-related genes and biomarkers to explore the molecular components of the disease and drug target engagement (see Section 11.5.1).

Exit interviews have been included as a recognised means of gaining better understanding of the patient experience of disease signs/symptoms and HRQoL impacts, and the IMP and trial procedures (30). Exit interviews are considered particularly valuable in a rare disease such as DLE where there is limited prior literature and knowledge about the patient experience.

13 Adverse events

13.1 Definition and classification of adverse events

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

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

13.2 Collection of adverse event reports

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

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.

Any potential AEs reported by the subjects during the exit interviews must be collected and documented in the CRO Exit Interview Potential AE Collection Form. The CRO must forward the CRO Exit Interview Potential AE Collection Form to the investigator within 24 hours. The investigator must check if these potential AEs are already recorded in the eCRF. If not, the investigator should contact the subjects for further information to ensure the potential AEs collected by the CRO are recorded in the eCRF as relevant (Section 13.3). If a potential AE qualifies as an SAE, the SAE must be reported as described in Section 13.4.

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 scalp, forehead, temple, malar, cheek, eyebrow, lower eyelid, upper eyelid, lower lip, upper

lip, chin, external ear, external nose, neck, trunk, arm, or leg. Additionally, the location should be reported as:

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

For target lesional/perilesional AEs, the identity of the affected target lesion should be recorded (target lesion 1 or 2).

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 first administration of IMP.

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

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

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

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 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 Safety at LEO using the e-mail address or fax number below:

Global Safety at LEO

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

Fax number: +45 7226 3287

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

Additionally, Global Safety 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 Safety at LEO (see contact details above) if the investigator becomes aware of them.

13.4.2 LEO reporting responsibilities

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

- The Investigator's Brochure for delgocitinib, edition 2.0 and subsequent updates.

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

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

For all non-US countries, the following reporting requirements apply: all SAEs which are assessed as causally related to the IMP(s) **by either the investigator or LEO** (ICH E2A Guideline), and which are unexpected (Suspected, Unexpected Serious Adverse Reactions [SUSARs]), are subject to expedited reporting to regulatory authorities and/or IEC(s)/IRB(s) according to the current applicable legislation in the concerned countries. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

13.5 Other events that require expedited reporting

13.5.1 Pregnancy

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

The completed Pregnancy Forms must be faxed or scanned and e-mailed to Global Safety at LEO. 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 11 is considered an AE of special interest (AESI) in this trial based on observations from a trial with delgocitinib cream in subjects with AD. Eczema herpeticum is a known risk for AD patients, but is not expected in DLE patients. If this AESI is observed, the investigator must provide additional details to be recorded in the eCRF. An AESI may be serious (requiring expedited reporting, Section 13.4) or non-serious.

Panel 11: Adverse event of special interest

Adverse event of special interest	**Additional information to be provided**
Eczema herpeticum.	Skin findings: • Lesion type. • Disseminated/localised. • 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 double the recommended quantity of IMP specified in this protocol in Section 9.2. An overdose is either accidental or intentional.

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

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

13.6.4 Misuse

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

The term 'misuse' must be recorded on the AE form in the eCRF. In addition, AEs originating from misuse must be recorded as separate events. 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 recorded on the AE form in the eCRF. In addition, AEs originating from abuse must be recorded as separate events. 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 screening, must be reported as an (S)AE in accordance with Sections 13.3 and 13.4.

13.7 Follow-up for final outcome of adverse events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). Once a subject leaves the clinical trial, the investigator should follow up on the outcome of all non-serious AEs classified as of possible/probable 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 from which the subject cannot be expected to recover during the trial or the safety follow-up periods, for example chronic or stabilised conditions, the final outcome should be reported as 'not recovered'. In addition, a statement that the SAE has stabilised or is chronic should be added to the narrative description of the SAE on the SAE form.

13.8 Handling of an urgent safety measure

An urgent safety measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined as *"...the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard."* (31).

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

This trial aims to achieve a total of 36 subjects completing the trial according to the protocol. Assuming a drop-out rate of 20%, a total of 45 subjects will be randomised. The screening failure rate is expected to be approximately 20%.

With 36 subjects completing the trial, a within-subject comparison of lesion-specific IGA scores according to the primary endpoint will detect a treatment difference with at least 90% power, assuming a probability of clearance of 5% for vehicle and 35% for delgocitinib cream. The power calculation is based on a Wald contrast test for equality of clearance probabilities evaluated at a 5% significance level.

14.2 Trial analysis sets

All subjects screened in the trial will be accounted for in the CTR.

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

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

- Receive no treatment with the IMPs.
- Do not complete the trial up to and including the Week 6 visit.
- Fail to provide efficacy data at the Week 6 visit.
- Are known to have used the wrong IMP on 1 or both target lesions.
- Do not fulfil the disease-defining inclusion criteria (that is, inclusion criteria no. 3-6).

Further exclusion of subjects or subject data will be decided upon after a blind review of the data, reviewing all the remaining in- and exclusion criteria, but focusing on concomitant medication that may affect DLE and also considering compliance and violations of visit windows.

A safety analysis set will be defined as all subjects who received IMP.

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

14.3 Statistical analysis

14.3.1 Disposition of subjects

The reasons for discontinuation of IMP or withdrawal from trial will be presented for all randomised subjects.

14.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects by site. Lesion-specific baseline characteristics will be presented for all randomised subjects by site and treatment.

14.3.3 Exposure and treatment compliance

The duration of exposure to treatment will be calculated as the number of days from the date of first application of IMPs to the date of last application of IMPs, both days included. Exposure will be presented for the FAS as days of exposure.

Drug accountability data will be calculated by subtracting the weight of the used tubes from the mean normal weight of full tubes. Average total usage will be presented for each treatment for the entire treatment period.

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

Treatment compliance will be presented for the safety analysis set for each treatment via the percentages of missed and/or excessive applications, and applications of wrong IMP.

14.3.4 Analysis of primary endpoint

The efficacy of delgocitinib cream compared with vehicle will be analysed in a within-subject comparison of lesion-specific treatment success (defined as an IGA score of 0 or 1 at Week 6) using McNemar's test.

The PP analysis set will be the primary analysis set for the primary endpoint. The analysis will be repeated on the FAS as a sensitivity analysis.

14.3.5 Analysis of secondary endpoints

Within-subject comparisons of the numbers of lesion-specific, treatment-related AEs will be done by treatment using a Wilcoxon signed rank test.

Within-subject comparisons of lesion-specific binary endpoints (≥2-point reduction in erythema score, and ≥2-point reduction in IGA score from baseline to Week 6) to assess treatment difference will be done by McNemar's test.

Within-subject comparison of lesion-specific erythema score and total skin disease activity score to assess treatment difference at Week 6 will be done by a Wilcoxon signed rank test.

The PP analysis set will be the primary analysis set for the secondary endpoints. The analysis will be repeated for the FAS as a sensitivity analysis.

14.3.6 Analysis of exploratory endpoints

14.3.6.1 Analysis of exploratory efficacy endpoints

Within-subject comparisons of lesion-specific binary endpoints (PaGA score of 0 or 1 at Week 6, and ≥2-point reduction in PaGA score from baseline to Week 6) to assess treatment difference will be done by McNemar's test.

Within-subject comparisons of lesion-specific IGA, PaGA, scaling/hyperkeratosis, oedema/infiltration, dyspigmentation, scarring/atrophy, total skin disease damage score, and total skin lesion disease score to assess treatment difference at Week 6 will be done by a Wilcoxon signed rank test.

The PP analysis set will be the primary analysis set for exploratory endpoints. The analysis will be repeated for the FAS as a sensitivity analysis.

14.3.6.2 Analysis of subject assessments

The DLQI and PaGA scores will be summarised using descriptive statistics. The exploratory endpoints concerning PaGA will be analysed as described in Section 14.3.6.1.

The exit interviews will be reported separately (see Section 14.3.6.3).

14.3.6.3 Exit interviews

The qualitative exit interviews will be audio-recorded, transcribed verbatim, and translated into English for analysis. Qualitative, thematic analysis methods will be used to analyse the verbatim transcripts. The results and analysis of the exit interviews will be reported separately from the CTR.

14.3.7 Analysis of pharmacodynamics and biomarkers

The full results from the pharmacodynamics/biomarker analysis of all skin samples will be described separately in an addendum to the CTR. A summary of the results will be included in the CTR if available before finalisation of the CTR.

14.3.8 Exploratory analyses

To assess the effect of delgocitinib cream compared with vehicle over time, within-subject comparisons of lesion-specific clearance according to IGA will be done by McNemar's test at baseline and at Weeks 2, 4, and 8. This analysis will be done on both the PP analysis set and the FAS.

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

Treatment-emergent AEs will be summarised; however, all AEs recorded during the trial will be included in subject data listings. An event will be considered treatment-emergent if started after the first application of IMP, or if started before the first application 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. The number of lesion-specific AEs will be tabulated by treatment. The number of lesions with lesion-specific AEs will be cross-tabulated within subject by treatment. The percentage of lesions with AEs will be compared between treatments by McNemar's test.

The severity for each type of AE will be tabulated. 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 severity for each type of lesion-specific AE will be tabulated by treatment.

The causal relationship to IMP for each type of AE will be tabulated. Where the investigator has provided several causality assessments for a given type of AE, the information provided in the last AE report will be used for the final causality assessment. The rationale is that by the time the last AE report is completed, the investigator will be in possession of most information and should be able to provide their best causality assessment.

Related AEs are defined as AEs for which the investigator has not described the causal relationship to IMP as 'not related'. The number of related AEs and the number of subjects with each type of related AE will be tabulated. The number of lesion-specific, related AEs will be cross-tabulated within subject by treatment. The number of lesions with lesion-specific, related AEs will be tabulated by treatment. The percentage of lesions with related AEs will be compared between treatments by McNemar's test.

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

AESIs and AEs leading to withdrawal from trial or discontinuation of IMP will be listed.

14.3.9.2 Vital signs

The change in vital signs (blood pressure, peripheral pulse, body temperature) from baseline (Day 1) to Week 6 will be summarised as mean, standard deviation (SD), median, and minimum and maximum values.

14.3.9.3 Clinical laboratory evaluation

The change in each of the laboratory parameters from baseline (Day 1) to Week 6 will be summarised as mean, SD, median, and 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. A shift table will be produced showing the categories at baseline (Day 1) against those at Week 6.

Subjects with laboratory parameters outside the reference range will be listed.

14.3.10 Interim analysis

No interim analysis is planned.

14.3.11 General principles

All significance tests will be 2-sided using the 5% significance level. All tests will be interpreted exclusively in a descriptive manner, i.e. independently of other tests. All confidence intervals will be presented with 95% degree of confidence, unless otherwise specified.

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

Categorical data will be summarised using the number and percentage of subjects in each category. Lesion-specific categorical data will be summarised by cross-tabulation within subject by treatment. Continuous data will be summarised using the mean, median, SD, and 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.

14.3.12 Handling of missing values

Missing values will be assumed missing at random and will not be imputed.

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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 Harmonised Tripartite Guideline for Good Clinical Practice, E6 (R1)).

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 11.4.4.2).

Serious adverse event definition

An SAE is any untoward medical occurrence that

- Results in death.
- Is life-threatening.

- Requires in-patient 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.

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

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

Appendix 3: Trial governance considerations

Appendix 3A: Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki (32) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (33).
- Current version of applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines (34).
- EU's General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

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

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

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

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

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

Appendix 3B: Informed consent process

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

The subject's signed and dated informed consent to participate in the clinical trial will be obtained prior to any clinical trial-related procedure being carried out in accordance with ICH-GCP (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 required.

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

Subject card
At screening, subjects will be provided with a card stating that they are participating in a clinical trial and which contains contact addresses and telephone numbers of relevant trial site staff including the number for the investigator in case of emergency situations. The subject card also includes a local telephone number for the emergency unblinding CRO to be used if the investigator or delegated site staff cannot be reached or if unblinding in the IRT system 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, ethnicity, age, gender, health condition, medical history, test results, etc.) which shall be collected as part of the clinical trial and processed during and after trial completion.

Personal data collected as part of the clinical trial will be transferred to/from the institution/investigator, LEO 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 and dated by medically qualified investigators.

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

- 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.
- Assigned kit number.
- The fact that the subject is participating in a clinical trial in DLE including treatment with delgocitinib cream and vehicle for 6 weeks.
- 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 trial processes and data have been evaluated. The main risk is recruitment problems, as DLE is a rare disease. This risk will be addressed by thorough feasibility analysis during the trial planning phase.

Other identified risks are:

- Inconsistency within the primary endpoint data due to IGA inter-rater variability.
- Accidental investigator unblinding due to slight differences in colour between the 2 IMPs.
- Accidental use of the wrong IMP on 1 or both target lesions.

Risk mitigation activities to ensure data quality and subject safety include:

- To ensure consistent efficacy assessments (IGA), all assessors will receive training before starting the trial. Whenever possible, the efficacy assessments will be made by the same investigator at each visit for a given subject to reduce inter-rater variability.
- To avoid unblinding, sites will be required to assign a staff member who is not involved in clinical assessments to apply the first IMP doses at the baseline visit.

- To ensure that the subjects apply the IMPs to the correct lesions throughout the trial, the subjects will receive a body diagram illustrating the location and assigned treatment of each target lesion at the baseline visit as a reference/reminder.

In addition, to ensure consistent AE monitoring and avoid duplicate AE reports, CRO staff conducting the exit interviews will be properly trained to detect and report any AEs that might be reported during these interviews (Section 13.2).

Throughout the trial, regular data quality review meetings will be held to ensure continuous improvement of data quality and prevention of mistakes. During monitoring visits at 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 electronically to LEO or designee (e.g. laboratory data). The investigator or staff authorised by the investigator will enter subject data into the eCRF. Data recorded in the eCRF will be accessible to the trial site and LEO personnel immediately after entry. The eCRF must be maintained in an up-to-date state by the trial site at all times.

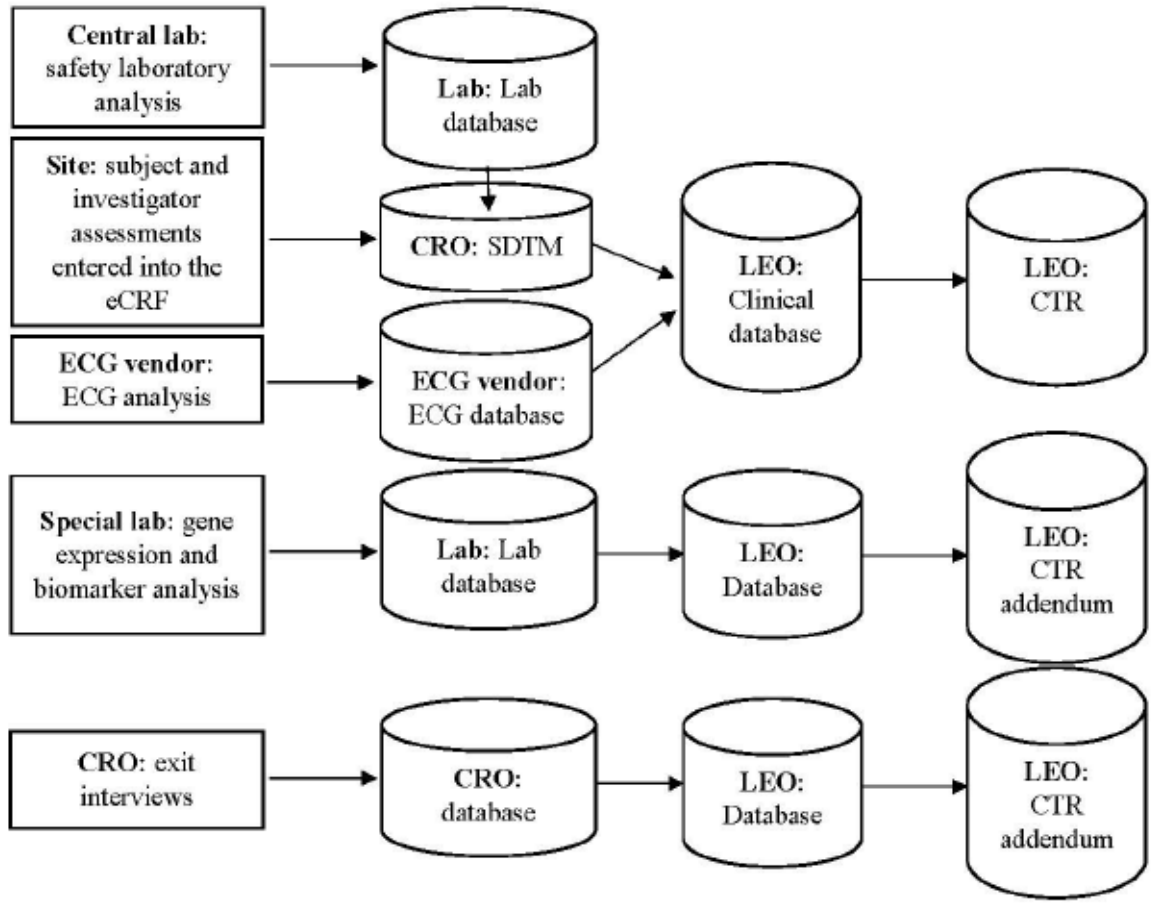
The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRF pages used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after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

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

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

Transmissions of electronic data from external data providers to the clinical database are illustrated in Panel 12.

Panel 12: Transmission of electronic data



Abbreviations: CRO = contract research organisation; CTR = clinical trial report; ECG = electrocardiogram; eCRF = electronic case report form; SDTM = study data tabulation model.

Archiving of trial documentation

The investigator at each trial site must make arrangements to store the essential trial documents, including the investigator trial file (34). 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 for all screened subjects at the trial site. This is done after completion of the trial and before access to the eCRF is revoked. Audit trail information will be included. eCRFs must be available for inspection by authorised representatives from LEO, 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 our Position on Public Access to Clinical Trial Information no later than 12 months after trial completion. Trial results may also become reported in www.ClinicalTrials.gov, www.clinicaltrialsregister.eu and national data registries in accordance with applicable law and regulations after clinical trial completion or premature termination.

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 LEO website.

Publications
In addition to making the results available on clinical registries as described above, peer-reviewed publications (congress abstracts and posters and journal publications) may be considered for this exploratory clinical trial. Should peer-reviewed publications be pursued, because this a multi-centre trial, the first publication will be a joint multi-centre publication. Multi-centre publications will be prepared in collaboration between LEO and the members of a writing committee, which shall be appointed by LEO.

Following such a multi-centre publication, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, provided that the identity of the subjects is not revealed and their consent has been obtained, subject to the following notice requirements.

Prior to submitting or presenting a manuscript related to the clinical trial to a publisher, reviewer, or other outside person, the investigator shall provide to LEO a copy of all such manuscripts, and LEO shall have rights to review and comment. Upon the request of LEO, the investigator shall 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, delay the publication or presentation to allow LEO to protect its inventions and other intellectual property rights described in any such manuscripts. In case the first multi-centre publication is still ongoing and has not been made public at the time of notification, LEO and the writing committee 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 Good Publication Practice (GPP3) standards.

LEO complies with 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 (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), and the joint position statement by the American Medical Writers Association (AMWA), the European Medical Writers Association (EMWA), and the International Society for Medical Publication Professionals (ISMPP) on disclosure of information about clinical trials, trial results and authorship. LEO also follows the CONSORT reporting guidelines (25).

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 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 to each target lesion 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: Justification for eligibility criteria

Inclusion criteria		
No.	**Short form of inclusion criteria**	**Justification**
1	Signed and dated informed consent has been obtained prior to any protocol-related procedures.	Requirement in accordance with ICH-GCP.
2	Age 18-70 years.	To avoid including vulnerable subjects.
3	Histopathological findings (current or previous) consistent with clinical diagnosis of DLE.	To ensure relevant target population.
4	Unequivocal clinical diagnosis of 2 active DLE target lesions that are less than 6 months old and amenable for clinical evaluation.	To ensure relevant target population with lesions suitable for treatment, i.e. lesions with reversible DLE activity signs.
5	Target lesion IGA score of at least moderate severity at screening and baseline.	To ensure that the subject has a severity of disease that makes assessment of improvement possible.
6	Target lesion erythema score of at least 2 at screening and baseline.	To ensure that the subject has a severity of disease that makes assessment of improvement possible.
7	For subjects taking hydroxychloroquine or chloroquine: No abnormal findings at the latest routine ophthalmologic examination, and no routine ophthalmologic examination is planned during the trial.	To prevent interference with safety endpoints.
8	Female subjects of childbearing potential must use a highly effective form of birth control throughout the trial and at least for 2 weeks after last administration of IMP.	To exclude any risk for the occurrence of genotoxicity/teratogenicity/fetotoxicity.
9	Prospective ability to attend all scheduled trial visits.	To ensure relevant target population and minimise the amount of missing data.

Exclusion criteria		
No.	**Short form of exclusion criteria**	**Justification**
1	Target lesion dyspigmentation score of 2 at screening or baseline.	To ensure that the subject does not have a high degree of damage of disease that makes assessment of improvement impossible.
2	Target lesion scarring/atrophy score of 2 at screening or baseline.	To ensure that the subject does not have a high degree of damage of disease that makes assessment of improvement impossible.
3	Target lesion scarring alopecia score of greater than 0 in scalp lesions at screening or baseline.	To ensure that the subject does not have a high degree of damage of disease that makes assessment of improvement impossible.

4	Medical history of SLE with clinically significant organ involvement (ACR SLE criteria no. 6 to 9).	For the safety of the subjects and to prevent interference with efficacy and safety endpoints.
5	Subjects with unstable or significant SLE disease activity findings that would interfere with the trial evaluation, completion, and/or procedures per the investigator's discretion.	For the safety of the subjects and to prevent interference with efficacy and safety endpoints.
6	Other skin conditions at screening or baseline that would interfere with evaluation of DLE.	To prevent interference with efficacy and safety endpoints.
7	Systemic immunosuppressive/immunomodulating therapy within 4 weeks prior to baseline.	For the safety of the subjects and to prevent interference with efficacy and safety endpoints.
8	Systemic prednisolone over 7.5 mg/day or changed dose within 4 weeks prior to baseline.	For the safety of the subjects and to prevent interference with efficacy and safety endpoints.
9	Treatment with oral antimalarial drugs and/or drugs known to interact with antimalarials.	For the safety of the subjects and to prevent interference with efficacy and safety endpoints.
10	Treatment with topical corticosteroids, calcineurin inhibitors, and phosphodiesterase-4 inhibitors within 2 weeks prior to baseline.	For the safety of the subjects and to prevent interference with efficacy and safety endpoints.
11	Use of systemic antibiotics or cutaneously applied antibiotics on the target lesions within 2 weeks prior to baseline.	For the safety of the subjects and to prevent interference with efficacy and safety endpoints.
12	UV therapy or excessive sun exposure within 2 weeks prior to baseline.	To prevent interference with efficacy and safety endpoints.
13	Any procedure impairing the skin barrier (e.g. incision) within 2 cm from the border of any of the target lesions within 4 weeks prior to baseline.	To prevent interference with efficacy and safety endpoints.
14	Receipt of live (attenuated) vaccines within 4 weeks prior to baseline.	For the safety of the subjects and to prevent interference with efficacy and safety endpoints.
15	Treatment with any marketed biological therapy or investigational biologic agents.	For the safety of the subjects and to prevent interference with efficacy and safety endpoints.
16	Treatment with any non-marketed substance within 4 weeks prior to baseline.	For the safety of the subjects and to prevent interference with efficacy and safety endpoints.
17	Unstable or fluctuating use of tobacco within 1 month prior to screening.	To prevent interference with efficacy and safety endpoints.
18	History of any active skin infection within 1 week prior to baseline.	For the safety of the subjects.
19	Clinically significant infection within 4 weeks prior to baseline.	For the safety of the subjects.

20	Tuberculosis requiring treatment within 12 months prior to screening and/or subjects with a positive blood test for tuberculosis at screening.	For the safety of the subjects.
21	Immunosuppressed or immunocompromised subjects.	For the safety of the subjects.
22	Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.	For the safety of the subjects.
23	History of cancer.	For the safety of the subjects.
24	Any disorder which is not stable and could affect the safety of the subject throughout the trial, influence the findings, or impede the subject's ability to complete the trial.	For the safety of the subjects and to prevent interference with efficacy and safety endpoints.
25	Any abnormal finding which may put the subject at risk, or influence the results or the subject's ability to complete the trial.	For the safety of the subjects and to prevent interference with efficacy and safety endpoints.
26	Positive HIV antibody, hepatitis B surface antigen, or hepatitis C virus antibody serology at screening.	For the safety of the subjects.
27	Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level more than 2 times ULN and/or a serum creatinine level more than 1.5 times ULN at screening.	For the safety of the subjects.
28	Known or suspected hypersensitivity to any component(s) of the IMP.	For the safety of the subjects.
29	Current participation in any other interventional clinical trial.	To prevent interference with efficacy and safety endpoints.
30	Previous randomisation in this clinical trial.	To ensure data integrity.
31	Previously randomised in a clinical trial with delgocitinib (LEO 124249).	To ensure data integrity.
32	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.	For the safety of the subjects and to ensure compliance with trial procedures and proper quality of the data to be collected.
33	Subjects who in the opinion of the investigator are likely to be non-compliant or unable to understand the trial and give adequately informed consent.	Requirement in accordance with ICH-GCP.
34	Employees of the trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.	Requirement in accordance with ICH-GCP.
35	Subjects who are legally institutionalised.	Requirement in accordance with ICH-GCP.

36	Female subjects who are pregnant or lactating.	For the safety of the unborn/newborn child.

Appendix 5: Contact list

Contact details for the clinical project manager, appointed CRA, sponsor's medical expert, and the national coordinating investigators 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

Signatory investigator

Margitta Worm, Univ. Prof. Dr. Med.
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Campus Charité Mitte
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Telephone: +49 (30) 450 518 105

Appendix 6: American College of Rheumatology revised criteria for classification of systemic lupus erythematosus (1997 update of the 1982 criteria) (26)

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion 1. *OR* 2. Pericarditis--documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed 1. *OR* 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance 1. *OR* 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia--with reticulocytosis 1. *OR*

Criterion	Definition
	2. Leukopenia--< 4,000/mm^3 on ≥ 2 occasions 1. OR 3. Lyphopenia--< 1,500/ mm^3 on ≥ 2 occasions 1. OR 4. Thrombocytopenia--<100,000/ mm^3 in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer 1. OR 2. Anti-Sm: presence of antibody to Sm nuclear antigen 1. OR 3. Positive finding of antiphospholipid antibodies on: 1. 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. 2. a positive test result for lupus anticoagulant using a standard method, or 3. 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Appendix 7: Cutaneous Lupus Erythematosus Disease Area and Severity Index (27)

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

activity ⟷ damage

Extent ↕

Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 … absent 1 … scarring 2 … severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

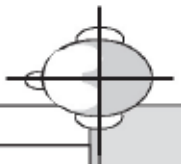
Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient … tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia



Recent Hair loss (within the last 30 days /as reported by patient)	
1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

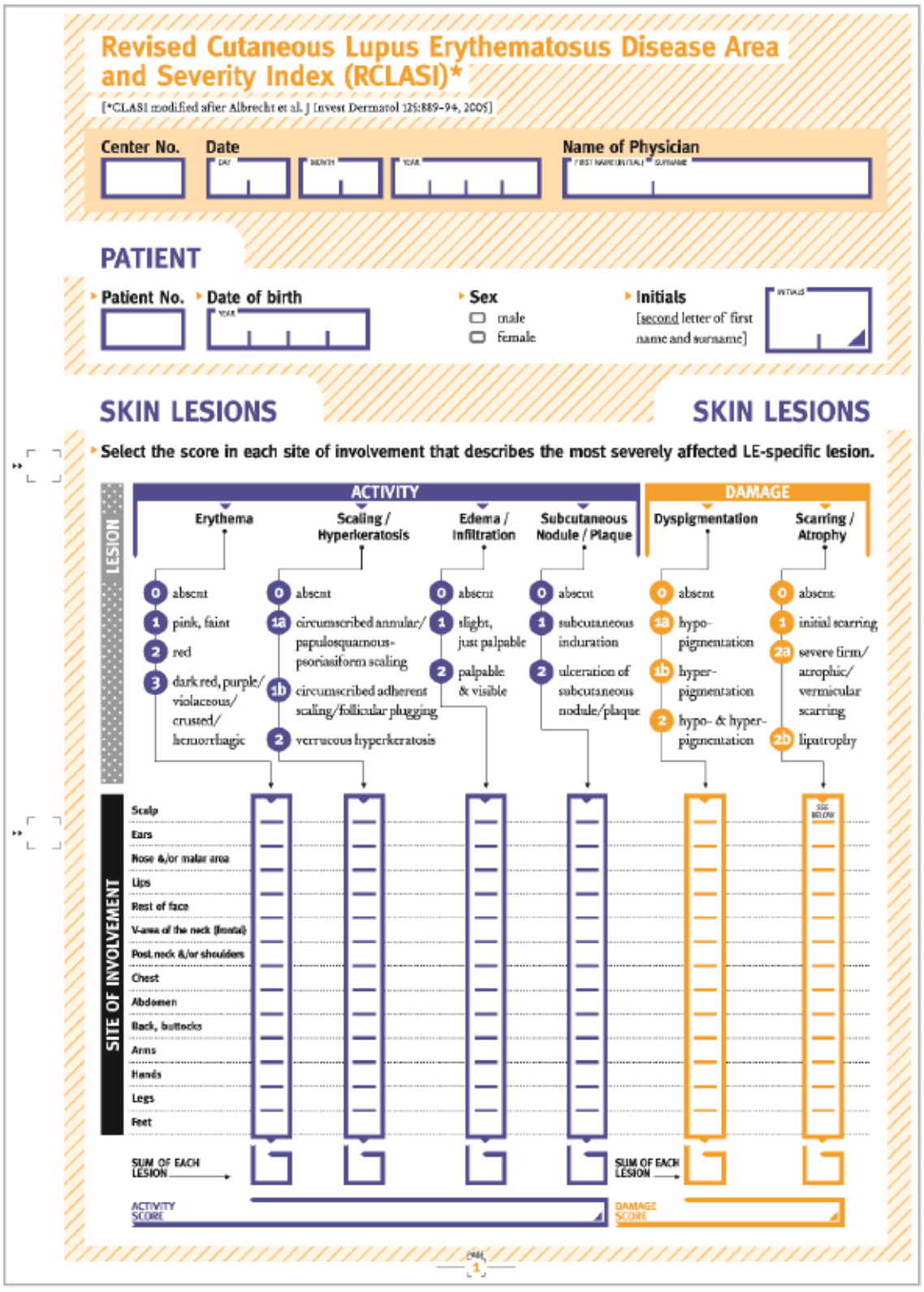
Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score (For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)		Total Damage Score (For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)	

Figure 1
Cutaneous LE Disease Area and Severity Index (CLASI)

Appendix 8: Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index (28)



MUCOUS MEMBRANE LESIONS

Select the score in each mucous membrane location that describes the most severely affected LE-specific lesion.

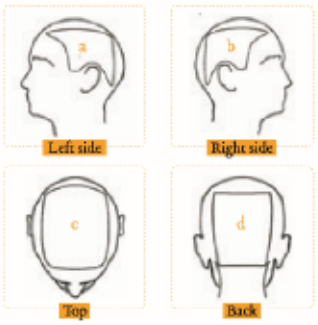
LESION	ACTIVITY: Erythematous Lesion	ACTIVITY: Keratotic Lesion	ACTIVITY: Erosion/ Ulceration
	0 absent 1 erythematous lesion	0 absent 1 white, lichen planus-like keratotic lesion	0 absent 1 erosion 2 ulceration
SITE OF INVOLVEMENT: Buccal mucosa			
Hard and soft palate			
Other mucous membranes			
SUM OF EACH LESION →			

ACTIVITY SCORE

ALOPECIA

[**Alopecia Score modified after Olsen et al. J Am Acad Dermatol 51:440–447, 2004]

DAMAGE



Scarring Alopecia Please estimate the percentage (0–100%) of scarring alopecia in each of the four areas (a, b, c, d) using the above diagram**:

a) Left side: _____ %
b) Right side: _____ %
c) Top: _____ %
d) Back: _____ %

Calculate the scarring alopecia score (using the estimated percentages from above)**:

a) Left side: 'estimated percentage' x .18 = _____ %
b) Right side: 'estimated percentage' x .18 = _____ %
c) Top: 'estimated percentage' x .40 = _____ %
d) Back: 'estimated percentage' x .24 = _____ %
Please add a + b + c + d: _____ %

Choose the adequate category for the total sum of a, b, c, & d:

0 absent
1 < 5%
2 5–9%
3 10–24%
4 25–49%
5 50–74%
6 75–100%

DAMAGE SCORE

TOTAL DAMAGE SCORE

For the total Damage Score please add up the scores of the right side i.e. for Skin lesions and Alopecia (scarring).

ALOPECIA

ACTIVITY

Diffuse Alopecia (clinically not scarred)

0 absent
1 slight diffuse effluvium
2 marked diffuse effluvium with partly visible scalp
3 severe diffuse effluvium affecting the whole scalp

'Lupus Hair' = 'Wooly Hair' (clinically not scarred)

0 absent
3 thin, weakened hairs that easily fragment above the surface of the scalp (especially at the anterior hairline &/or at the periphery of the scalp)

ACTIVITY SCORE

TOTAL ACTIVITY SCORE

For the total Activity Score please add up the scores of the left side i.e. for Skin lesions, Mucous membrane lesions, and Alopecia (non-scarring).

Appendix 9: Protocol amendment history

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

Summary of changes table for amendment 1 (15-May-2019)

Section no. and name	Description of change	Brief rationale
Protocol synopsis (Statistical methods)	The description of the primary endpoint is corrected from 'an IGA score of 0 or 1 at Week 6 and a ≥2-point reduction from baseline' to 'an IGA score of 0 or 1 at Week 6'.	To align the wording of the primary endpoint with that in Section 6 and avoid ambiguity.
4 Schedule of trial procedures	ECG was added at the unscheduled visit.	To clarify that the investigator can record an ECG at the unscheduled visit if considered relevant.
4 Schedule of trial procedures	A urine pregnancy test was added at the follow-up visit.	To rule out (or identify) any pregnancy during the trial up to and including the follow-up visit.
4 Schedule of trial procedures	An '(X)' and a new footnote g) is added for CLASI and RCLASI at baseline to specify that scarring alopecia will be scored for each target lesion at screening and baseline (applicable to scalp lesions only).	To specify collection of the data used to evaluate exclusion criterion no. 3.
5.2 Experience with investigational	The reference to the investigator's brochure is updated from version 1.0 to 2.0, and the numbers of completed clinical trials and subjects exposed to	The investigator's brochure has been updated since finalisation of the protocol.

Section no. and name	**Description of change**	**Brief rationale**
medicinal product	delgocitinib are updated accordingly.	
5.4 Ethical considerations	It is added that a urine pregnancy test will be taken at the follow-up visit.	To rule out (or identify) any pregnancy during the trial up to and including the follow-up visit.
5.4 Ethical considerations	It is added that no contraceptive measures are required for male subjects in this trial.	To clarify ethical considerations around contraception.
8.3 Exclusion criteria	The exclusion criterion regarding use of products containing Hypericum perforatum (St John's Wort) is deleted (exclusion criterion no. 15 in version 2.0 of the protocol).	This exclusion criterion was included in the original protocol by error and is not considered relevant for this trial. Hypericum perforatum is an inducer of the liver enzymes which metabolise delgocitinib, but no or negligible systemic absorption of delgocitinib is expected in this trial.
8.4 Screening and screening failures	It is added that each subject can only be re-assessed for eligibility once.	To define the upper limit for the number of re-assessments of eligibility.
8.4 Screening and screening failures	Inclusion criterion no. 7 is added to the list of inclusion criteria for which re-assessment will be allowed.	Since DLE is a rare disease, and the number of eligible patients is limited, subjects for whom a routine ophthalmologic examination is planned during the trial will be allowed to be re-assessed for eligibility after the examination.

Section no. and name	**Description of change**	**Brief rationale**
8.4 Screening and screening failures	Exclusion criterion no. 15 (in version 2.0 of the protocol) is deleted from the list of exclusion criteria for which re-assessment of eligibility will be allowed.	This exclusion criterion was included in the original protocol by error and is not considered relevant for this trial.
9.2 Administration of IMP	Information about the IRT system assigning the kit number is moved to Section 9.3.	This text belongs in Section 9.3 and is moved to replace the previous, incorrect text (see row below).
9.3 Treatment assignment	Deletion of incorrect text: ~~Eligible subjects will receive a randomisation code number in the order of their randomisation to treatment at the trial site.~~ ~~Each trial site will receive a list of 12 consecutive randomisation code numbers. The randomisation code numbers will contain 5 digits, starting from 10101 at the first trial site in the first country, from 10201 at the second trial site in the first country, from 20101 at the first trial site in the second country, from 20201 at the second trial site in the second country, and so forth.~~	This text was included in the original protocol by error. The subjects will not have randomisation code numbers; instead the interactive response technology system will assign the kit number.

Section no. and name	**Description of change**	**Brief rationale**
	~~During the trial, the randomisation lists will be kept secure by LEO, inaccessible to all staff involved with the conduct or administration of the trial, until the trial is unblinded.~~ In addition, information about the IRT system assigning the kit number is moved from Section 9.2 to Section 9.3.	
9.7 Prohibited medication and procedures	It is added that changes in dose or discontinuation of medications or procedures listed as prohibited should only be done for medical reasons, not trial-related reasons.	To clarify that medically indicated treatments should never be changed or discontinued only to allow the subject to participate in the trial.
9.7 Prohibited medication and procedures	Hypericum perforatum is deleted from the list of prohibited medication.	This was included as prohibited medication in the original protocol by error and is not considered relevant for this trial. Hypericum perforatum is an inducer of the liver enzymes which metabolise delgocitinib, but no or negligible systemic absorption of delgocitinib is expected in this trial.
10.2.1 Discontinuation of IMP	It was added that AEs that, in the opinion of the investigator or sponsor's medical expert, contraindicate further dosing include unacceptable worsening of DLE symptoms.	To clarify that subjects with unacceptable worsening of DLE (in the opinion of the investigator or sponsor's medical expert) should be discontinued from IMP, after which the subject can be treated at the investigator's discretion.

Section no. and name	**Description of change**	**Brief rationale**
10.2.1 Discontinuation of IMP	One of the reasons for permanent discontinuation of IMP is corrected as follows: Confirmed ALT and/or AST >5×ULN ~~(for more than 2 weeks)~~.	IMP will be discontinued immediately in case of confirmed ALT and/or AST >5×ULN, as this could indicate e.g. toxic hepatitis.
11.2.5 Classification of systemic lupus erythematosus	It is added that any abnormal test results found as part of the classification of SLE will be followed up at the discretion of the investigator.	To clarify handling of abnormal test results found during the classification of SLE.
11.4.4.1 Overview	Minimum sensitivity of the urine pregnancy test (25 mIU/mL) is added in footnote e) to Panel 10.	To specify the sensitivity of the pregnancy test as requested by the German authorities.
11.5.2 Non-invasive skin sampling	Patches for non-invasive skin sampling will be applied for 15 minutes (not 20 minutes).	Updated instructions for use from the manufacturer.
11.6.1.3 Exit interviews (optional, selected countries only)	Events reported by the CRO conducting exit interviews are referred to as 'potential AEs' rather than 'AEs'.	To clarify that events reported by the interviewers (who are not medically qualified) will not necessarily be regarded as AEs by the investigator.
11.6.3 Photography (optional)	It was deleted that photographs may undergo planimetric analysis to determine the area of the target lesions.	Planimetric analysis will not be performed under this protocol.
13.2	Events reported by the CRO conducting exit interviews are	To clarify that events reported by the interviewers (who are not medically

Section no. and name	**Description of change**	**Brief rationale**
Collection of adverse event reports	referred to as 'potential AEs' rather than 'AEs'.	qualified) will not necessarily be regarded as AEs by the investigator.
13.4.2 LEO reporting responsibilities	The reference safety information is updated to the investigator's brochure version 2.0.	The investigator's brochure has been updated since finalisation of the protocol.
14.3.4 Analysis of primary endpoint	The description of the primary endpoint is corrected from 'an IGA score of 0 or 1 at Week 6 and a ≥2-point reduction from baseline' to 'an IGA score of 0 or 1 at Week 6'.	To align the wording of the primary endpoint with that in Section 6 and avoid ambiguity.
14.3.5 Analysis of secondary endpoints	Wording of the secondary endpoints are corrected.	To align the wording of the secondary endpoints with that in Section 6.
14.3.6.1 Analysis of exploratory efficacy endpoints	Wording of the exploratory efficacy endpoints are corrected.	To align the wording of the exploratory endpoints with that in Section 6.
14.3.11 General principles	It is added that all tests will be interpreted exclusively in a descriptive manner, i.e. independently of other tests.	To clarify the general principles in the statistical analysis.
Appendix 3D Record keeping, quality control,	'Randomisation code number' is changed to 'Assigned kit number'.	This text was included in the original protocol by error. The subjects will not have randomisation code numbers; instead the interactive response

Section no. and name	**Description of change**	**Brief rationale**
and data handling		technology system will assign the required kit number.
Appendix 4 Justification for eligibility criteria	The exclusion criterion regarding use of products containing Hypericum perforatum (St John's Wort) is deleted (exclusion criterion no. 15 in version 2.0 of the protocol).	This exclusion criterion was included in the original protocol by error and is not considered relevant for this trial.
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarised.