Cover Page

Study title: A Phase 2a, Randomized, Double-Blind, Vehicle-Controlled, Single Site, Exploratory Trial to Assess the Effect of Delgocitinib Cream 20 mg/g on the Molecular Signature, Safety, and Efficacy in Adults With Frontal Fibrosing Alopecia
LEO Pharma number: EXP-2228
NCT number: NCT05332366
Date: 17-Nov-2021

A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, SINGLE SITE, EXPLORATORY TRIAL TO ASSESS THE EFFECT OF DELGOCITINIB CREAM 20 mg/g ON THE MOLECULAR SIGNATURE, SAFETY, AND EFFICACY IN ADULTS WITH FRONTAL FIBROSING ALOPECIA

PROTOCOL EXP-2228

FINAL

VERSION 2.0

17 November 2021

Sponsor:	LEO Pharma A/S Industriparken 55 DK-2750 Ballerup Denmark
Sponsor Medical Expert:	PPD MD, PhD; PPD Translational Medicine PPD
Sponsor Representatives:	PPD MD, PhD; PPD Translational Medicine PPD MD; PPD Medical Sciences PPD MSc Stat, PPD Medical Sciences PPD MSc Pharm, PPD Global Clinical Operations
Clinical Research Organization:	PPD

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL VERSION HISTORY

Version	Rationale for amendment	Main changes to the protocol
1.0 / 03 June 2021	Initial version	N/A
2.0 / 17 November 2021	To change the Sponsor Medical Expert	- Cover page and Signature page: The Sponsor Medical Expert was changed to PPD
	To address the following FDA recommendations for Cohort 1:	
	- To modify the safety monitoring during the open-label extension (OLE) so that subjects who initiate delgocitinib will be monitored similarly, whether they initiate delgocitinib during the OLE or the initial treatment period.	- Synopsis, Section 1.3 (Table 1), Section 4.1, Section 8.2.4, and Section 8.2.6: The phone call visits planned at Week 16 and Week 20 were changed to on-site visits. Therefore, subjects will come to the site on 9 occasions, including at Week 16 and Week 20. All assessments that were to be performed at the phone call visits will be done at the site. Some additional safety, efficacy, and other assessments were added at Week 16 and Week 20 visits.
	- To add the approximate dimension of the lesional target area and to specify that tape stripping will be optional.	- Synopsis, Section 1.3 (Table 1, footnotes c and k), Section 4.1, Section 8.1.7, Section 8.3, and Section 8.4.1: Clarifications added regarding selection of the lesional target area(s), including dimension. Clarifications added regarding which assessments could and could not overlap on the lesional target area(s). Specifications added for the tape stripping collection.
	- To evaluate thyroid function at screening	- List of abbreviations, Synopsis, Section 1.3 (Table 1), Section 5.2, and Section 8.2.4: Added thyroid-stimulating hormone (TSH) with reflex free T4 at screening and related exclusion criterion (Exclusion Criterion #14).
	- To allow treatment of the eyebrows, if affected	- Section 5.3 and Section 6.1: Clarified that all affected areas on the face/scalp can be treated, including the eyebrows, if affected. If eyebrows are treated, subjects should abstain

		from wetting them within 2 hours following IMP application.
	To add the outcome categories of adverse events (AEs).	- Section 8.5.4: Added the different outcome categories of AEs under a new section 8.5.4.3.
	To clarify that the Numerical Rating Scale questions (pruritus, burning sensation, and pain) will be specific to frontal fibrosing alopecia.	- Appendix C: Modified the NRS questions so that the three questions are specific to frontal fibrosing alopecia.
	To add the Innovaderm project team contact information for SAE reporting.	- Section 8.5.7: Added the Innovaderm project team e-mail address.
	To clarify that the use of systemic or topical treatment with minoxidil or systemic treatment with spironolactone is allowed if used for at least 6 months prior to Day 1 and continue on stable dosing during the study.	- Synopsis, Section 5.2, and Section 6.4.1, a note was added to specify that systemic treatment with minoxidil or spironolactone and topical treatment with minoxidil is allowed if used for at least 6 months prior to Day 1 and the subject agrees to continue using it on a stable dosing during the present study (Exclusion Criterion #19 and #20).
	To clarify the restrictions to be followed by the subjects under stable dose of topical minoxidil the day of the visits with regards to the application of topical product to the areas where the skin samples will be collected.	- Section 5.3, the following note was added: In addition, for the subjects who are on stable dose of topical minoxidil for at least 6 months prior to Day 1 and continue using it during the study, they should be instructed to not apply it on the areas where skin samples will be collected on the visit days before the visit.

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable local regulations. The principal investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the institutional review board (IRB)/research ethics board (REB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this trial have completed ICH GCP training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB/REB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/REB before the changes are implemented to the trial. All changes to the consent form will be IRB/REB approved.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and provide the necessary assurances that this trial will be conducted according to this protocol, applicable local regulations, and ICH GCP guidelines.

Sponsor:

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 18-Nov-2021 | 14:52:15 EST
D3356B702B464F3996DEFC44215D8354

18-Nov-2021 | 14:52:20 EST

PPD MD, PhD
PPD Translational Medicine
LEO Pharma A/S

Date (DD-MMM-YYYY)

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 22-Nov-2021 | 10:08:27 EST
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22-Nov-2021 | 10:08:39 EST

PPD MD, PhD
PPD Translational Medicine
LEO Pharma A/S

Date (DD-MMM-YYYY)

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 22-Nov-2021 | 07:55:53 PST
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22-Nov-2021 | 07:56:05 PST

PPD MD
PPD Medical Sciences
LEO Pharma A/S

Date (DD-MMM-YYYY)

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PPD
Signer Name: PPD
Signing Reason: I approve this document
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22-Nov-2021 | 10:58:08 EST

PPD MSc Stat
PPD Medical Sciences
LEO Pharma A/S

Date (DD-MMM-YYYY)

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
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PPD MSc Pharm
PPD Global Clinical Operations
LEO Pharma A/S

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SIGNATURE PAGE (Continued)

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7B587BB5D1784033A925A4345557A0A4

Scientific Affairs: 22-Nov-2021 | 11:40:46 EST

PPD BSc
PPD Scientific and Regulatory Affairs
Innovaderm Research Inc.

Date (DD-MMM-YYYY)

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 22-Nov-2021 | 12:42:58 EST
D96D4D3C2ADE46CEA93C89D6469C1E56

Biometrics: 22-Nov-2021 | 12:43:02 EST

PPD , MSc
PPD Biometrics
Innovaderm Research Inc.

Date (DD-MMM-YYYY)

PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator Name: PPD

Signature: PPD **Date:** 30-NOV-2021
(DD-MMM-YYYY)

Institution Name: PPD

By my signature, I agree to personally supervise the conduct of this trial at my site and to ensure its conduct in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, informed consent, institutional review board/independent ethics committee procedures, instructions from sponsor's representatives, ICH GCP guidelines, and applicable local regulations governing the conduct of clinical studies.

LIST OF ABBREVIATIONS

AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	antibody to hepatitis B core antigen
AST	aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BUN	blood urea nitrogen
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRA	clinical research associate
CRO	contract research organization
CXCL9	chemokine (C-X-C motif) ligand 9
CXCL10	chemokine (C-X-C motif) ligand 10
EASI	Eczema Area and Severity Index
EASI75	a 75% reduction in EASI score
ECG	Electrocardiogram
eCRF	electronic case report form
eHFSC	epithelial hair follicle stem cells
EDC	Electronic Data Capture
ET	early termination
FDA	Food and Drug Administration
FAS	full analysis set
FFA	frontal fibrosing alopecia
FFASS	Frontal Fibrosing Alopecia Severity Score
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	Hematocrit
HCV	hepatitis C virus
Hgb	Hemoglobin
HIV	human immunodeficiency virus
HFIP	hair follicule immune privilege
IB	Investigator Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
IMP	investigational medicinal product
INF	Interferon
IRB	institutional review board
JAK	Janus kinase

JT	Japan Tobacco Inc.
LDH	lactate dehydrogenase
LPP	lichen planopilaris
LPPAI	lichen planopilaris activity index
LTA	local tolerability assessment
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
NA	not applicable
NRS	Numerical Rating Scale
OLE	open-label extension
pDC	plasmacytoid dendritic cells
PDE-4	phosphodiesterase-4
PLT	Platelets
PP	per-protocol
PUVA	psoralen-UV-A
PT	preferred term
QC	quality control
RBC	red blood cell
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
STAT	signal transducer and activator of transcription
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UV	Ultraviolet
vIGA-AD TS	Validated Investigator Global Assessment for Atopic Dermatitis treatment success
WBC	white blood cell
WOCBP	women of childbearing potential
WHO	world health organization

1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor/Company: LEO Pharma A/S	**Name of Investigational Product:** Delgocitinib cream 20 mg/g	**Name of Active Ingredient:** Delgocitinib

Title of Trial:

A Phase 2a, Randomized, Double-Blind, Vehicle-Controlled, Single Site, Exploratory Trial to Assess the Effect of Delgocitinib Cream 20 mg/g on the Molecular Signature, Safety, and Efficacy in Adults with Frontal Fibrosing Alopecia

Phase of Development:

Phase 2a

Trial Site:

This trial will be conducted at 1 site located in the United States PPD Boston, MA).

Number of Subjects (planned):

- Cohort 1
  - Approximately 30 subjects with frontal fibrosing alopecia (FFA) will be randomized in this cohort.
- Cohort 2
  - Approximately 5 healthy postmenopausal female subjects will be included in this cohort.

Duration of Trial:

- Cohort 1
  - The maximum trial duration per subject is approximately 30 weeks, including up to 30 days for the screening period, 12 weeks for the vehicle-controlled treatment period, 12 weeks for the open-label extension (OLE), and approximately 2 weeks for the safety follow-up period.
- Cohort 2
  - The maximum trial duration per subject is approximately 6 weeks, including up to 30 days for the screening period, 1 day for the skin samples collection, and up to 14 days for the optional follow-up period.

Investigational Medicinal Product, Dosage, and Mode of Administration:

Delgocitinib cream 20 mg/g and matching vehicle (delgocitinib cream vehicle).

- Cohort 1
  - Subjects will be randomized in a 1:1 ratio on Day 1 to apply delgocitinib cream 20 mg/g or vehicle cream twice daily (BID) for 12 weeks during the vehicle-controlled treatment period.

Name of Sponsor/Company: LEO Pharma A/S	**Name of Investigational Product:** Delgocitinib cream 20 mg/g	**Name of Active Ingredient:** Delgocitinib

After the vehicle-controlled treatment period, subjects will continue into the OLE and will apply delgocitinib cream 20 mg/g BID for 12 weeks.

- Cohort 2

  - No investigational product will be administered in Cohort 2.

Objectives:

Primary:

The primary objective is:

- To assess molecular signature changes following topical application of delgocitinib cream 20 mg/g in subjects with FFA.

Secondary:

The secondary objective is:

- To evaluate the safety and tolerability of delgocitinib cream 20 mg/g following topical application in subjects with FFA during the vehicle-controlled treatment period.

Exploratory:

The exploratory objectives are:

- To evaluate the safety and tolerability of delgocitinib cream 20 mg/g during the OLE.
- To evaluate the preliminary efficacy of delgocitinib cream 20 mg/g following topical application in subjects with FFA.

Endpoints:

Primary Endpoint:

- Change in expression of chemokine (C-X-C motif) ligand 9 (CXCL9), chemokine (C-X-C motif) ligand 10 (CXCL10), and interferon (IFN)-γ from baseline to Week 12.

Secondary Endpoint:

- Number of treatment-emergent adverse events (TEAEs) from baseline to Week 12.

Exploratory Endpoints:

Exploratory safety endpoint:

- Number of TEAEs during the OLE (up to Week 26)

Exploratory efficacy endpoints during the vehicle-controlled treatment period:

- Change in Lichen Planopilaris Activity Index (LPPAI) score from baseline to Weeks 4, 8, and 12.
- Change in Frontal Fibrosing Alopecia Severity Score (FFASS) from baseline to Weeks 4, 8, and 12.
- Change in target area perifollicular erythema score from baseline to Weeks 4, 8, and 12.
- Change in target area perifollicular scale score from baseline to Weeks 4, 8, and 12.
- Change in pruritus Numerical Rating Scale (NRS) score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12.

Name of Sponsor/Company: LEO Pharma A/S	**Name of Investigational Product:** Delgocitinib cream 20 mg/g	**Name of Active Ingredient:** Delgocitinib

- Change in burning sensation NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12.
- Change in pain NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12.
- Proportion of subjects with a 3-point reduction* in pruritus NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12.
- Proportion of subjects with a 4-point reduction* in pruritus NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12.
- Proportion of subjects with a 3-point reduction* in burning sensation NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12.
- Proportion of subjects with a 4-point reduction* in burning sensation NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12.
- Proportion of subjects with a 3-point reduction* in pain NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12.
- Proportion of subjects with a 4-point reduction* in pain NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12.
- Change in target area hair counts/trichoscopy via fotofinder trichovision from baseline to Week 12.

Exploratory efficacy endpoints during the OLE:

- These efficacy outcomes will be measured at scheduled visits after Week 12: LPPAI, FFASS, target area perifollicular scale score, target area perifollicular erythema score, pruritus NRS, burning sensation NRS, pain NRS, and target area hair counts/trichoscopy via fotofinder trichovision.

* Note: Only subjects with a baseline NRS score ≥3 will be included in the respective endpoints on proportion of subjects with a 3-point reduction. Only subjects with a baseline NRS score ≥4 will be included in the respective endpoints on proportion of subjects with a 4-point reduction.

Trial Design:

A Phase 2a, randomized, double-blind, vehicle-controlled, single-site, exploratory trial of delgocitinib cream 20 mg/g in subjects with FFA.

The trial will consist of 2 cohorts: Cohort 1 will include approximately 30 subjects with FFA and Cohort 2 will include approximately 5 healthy postmenopausal female subjects. Both cohorts can be conducted in parallel.

Cohort 1:

All subjects will read and sign an informed consent form (ICF) prior to any trial-related activities being performed. Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be randomized into the trial. After a screening period of no more than 30 days (from Day -30 to Day -1), eligible subjects will be randomized (1:1) on Day 1 to apply delgocitinib cream 20 mg/g or vehicle cream BID for 12 weeks during the vehicle-controlled treatment period. All subjects who complete the vehicle-controlled treatment period will then continue into the OLE and apply delgocitinib cream 20 mg/g BID for 12 weeks. The OLE period will be followed by a 2-week safety follow-up period. For scheduled trial visits, subjects will come to the site on 9 occasions: screening, Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, and Week 26/early termination (ET).

Name of Sponsor/Company: LEO Pharma A/S	**Name of Investigational Product:** Delgocitinib cream 20 mg/g	**Name of Active Ingredient:** Delgocitinib

On Day 1, a lesional target area on the scalp (eg, frontal, periauricular, or temporal area) that will be treated with the investigational medicinal product (IMP) will be identified. To allow for the hair count/trichoscopy assessment and all samples collection (ie, skin biopsies, tape stripping, and skin swabs) the lesional target area should be approximately 3 cm x 6 cm (or equivalent). However, as tape strips can be collected from the same area where trichoscopy/hair counts is performed or can be collected adjacent/close to the lesional target area (refer to Section 8.3.2 for details), a smaller lesional target area may be acceptable. If needed, two small target areas (totalling approximately the same size) could also be selected to allow for skin samples collection and hair count/trichoscopy assessment. If two lesional target areas are selected, they should be of similar severity.

The following skin samples will be collected during the trial to assess molecular signature changes:

- Skin biopsies for transcriptomic and immunohistochemistry (IHC) analyses (n=3):
    - *Day 1:* 2 skin biopsies (4-mm) will be collected prior to the first IMP application (1 from a lesional hair follicle within the target area and 1 from a non lesional hair follicle [eg, on the occipital scalp]).
    - *Week 12:* 1 skin biopsy (4-mm) will be collected from a hair follicle within the lesional target area (outside the scar of previous biopsies).
- Skin swabs for microbiome analysis (n=3):
    - *Day 1*: 2 skin microbiome samples will be collected prior to the first IMP application (1 from the target area [lesional skin] and 1 from an uninvolved occipital scalp area).
    - *Week 12*: 1 skin microbiome sample will be collected at the same location of the lesional skin of the target area.
- Adhesive tape strips samples for transcriptomic analysis (n=3):
    - *Day 1*: skin tape strips will be collected prior to the first IMP application from lesional skin and from non lesional skin (eg, on the occipital scalp).
    - *Week 12*: skin tape strips will be collected at the same location of the lesional skin.

    Note: Every effort should be made to collect tape strip samples in all subjects however, adhesive tape strip collection is optional and will be collected per investigator's judgement (based on available skin area on the scalp).

Safety will be assessed by collecting adverse events (AEs), recording vital signs, performing complete and brief physical examinations, and evaluating clinical laboratory results and local tolerability assessments (LTA).

Efficacy will be assessed using LPPAI, FFASS, evaluation of the perifollicular erythema and perifollicular scale, pruritus NRS, burning sensation NRS, pain NRS, and hair counts/trichoscopy (eg, number of hairs, hair diameter, and hair density). Hair line measurements (ie, lateral canthus [right and left] to hairline, lower glabellar crease to hair line, top of frontalis muscle to hair line, and mid brow to hair line [right and left]) will also be done.

Medical photographs of the lesional target area and the entire scalp (including the frontal hair line and right and left hair line areas) will be taken with the fotofinder device during the trial.

Name of Sponsor/Company: LEO Pharma A/S	**Name of Investigational Product:** Delgocitinib cream 20 mg/g	**Name of Active Ingredient:** Delgocitinib

Cohort 2:

All subjects will read and sign an ICF prior to any trial-related activities being performed. Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be accepted into the trial. After a screening period of no more than 30 days (from Day -30 to Day -1), eligible subjects will be asked to come at the site for skin samples collection. Screening and skin samples collection on Day 1 can be performed on the same day (if subjects do not have a washout period) or on two separate visits, at the investigator's discretion. No investigational product will be administered in Cohort 2. For scheduled trial visits, subjects will come to the site on up to 3 occasions: screening, Day 1, and optional follow-up visit.

The following skin samples will be collected:

- Skin biopsies (n=2):
    - *Day 1:* 2 skin biopsies (4-mm) that include hair follicles will be collected on healthy skin at similar matched areas of subjects with FFA (ie, 1 from frontal scalp area and 1 from occipital scalp area)
- Adhesive tape strips (n=1):
    - *Day 1*: skin tape strips will be collected on non-hair bearing healthy skin at a similar matched area of subjects with FFA (ie, on the forehead, as close as possible to the frontal scalp area).
- Skin swabs for microbiome analysis (n=2):
    - *Day 1*: 2 skin microbiome samples will be collected on healthy skin at similar matched areas of subjects with FFA (ie, 1 from frontal scalp area and 1 from occipital scalp area).

For Cohort 2 only, safety will be assessed by review of any procedural complications and changes in health observed after skin samples collection.

Inclusion/Exclusion Criteria:

Inclusion criteria:

In order to be eligible to participate in this trial, a subject must meet all of the following criteria, either at the screening and Day 1 visits or only at one of the specified visits (screening or Day 1) as noted in the criterion:

Inclusion criteria for all subjects:

1. Subject is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any trial-related procedures.
2. Subjects must be willing to comply with all trial procedures and must be available for the duration of the trial.

Inclusion criteria for Cohort 1 only (subjects with FFA):

3. Male or female subject aged 18 years of age or older at the time of consent.
4. Female subject of childbearing potential has had a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
5. Subject has clinically confirmed diagnosis of FFA based on investigator's judgment.
6. Subject has a target area with a perifollicular erythema score ≥ 2 and a perifollicular scale score ≥ 2 at Screening and Day 1.

Name of Sponsor/Company: LEO Pharma A/S	**Name of Investigational Product:** Delgocitinib cream 20 mg/g	**Name of Active Ingredient:** Delgocitinib

7. For subject who uses make-up, moisturizers, creams, lotions, cleansers, and/or sunscreens on the face, subject has used the same product brands/types for a minimum period of 4 weeks prior to Day 1, agrees not to change brand/type or frequency of use throughout the trial, agrees not to apply those products on the treated area during the trial, and agrees not to use make-up, moisturizers, creams, lotions, cleansers, and/or sunscreens on the face on the clinic visit days before the visit.
8. Subject is willing to maintain a consistent hair style and hair style regimen, including shampoo and hair products (including hair dye, process, and timing to hair appointments), and to refrain from weaves or extensions throughout the course of the trial and for 4 weeks prior to Day 1.

   Note: Hair dying and shaving of scalp is allowed during the trial but not within 48 hours prior to a trial visit.
9. For female subject of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use an effective contraceptive method from at least 4 weeks prior to Day 1 until at least 4 weeks after the last IMP application. Effective contraceptive methods include hormonal contraceptives (eg, combined oral contraceptive, progesterone-only hormonal contraception [associated with or without inhibition of ovulation as the primary mode of action], patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s) (provided his vasectomy was performed ≥4 months prior to Screening), tubal ligation or a barrier method of contraception (eg, male condom, female condom, cervical cap, diaphragm, contraceptive sponge) in conjunction with spermicide.

   Note: Subjects must have been on a stable dose of hormonal contraceptives for at least 4 weeks before Day 1.

   Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the trial. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable.

   Note: A female subject of nonchildbearing potential is defined as follows:

   - Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
   - Female subject who has had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause

<u>Inclusion criteria for Cohort 2 only (healthy subjects):</u>

10. Female subject aged 45 years of age or older at the time of consent.
11. Female is postmenopausal as defined below:
    - Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
    - Female subject who has had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause.
12. Subject is in good general health, according to the investigator's judgment based on vital signs, medical history, and brief physical examination.

Name of Sponsor/Company: LEO Pharma A/S	**Name of Investigational Product:** Delgocitinib cream 20 mg/g	**Name of Active Ingredient:** Delgocitinib

Exclusion criteria:

A subject who meets any of the following criteria at the screening and/or Day 1 visits, as applicable, will be excluded from participation in this trial:

Exclusion criteria for all subjects:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the trial.
2. Subject has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
3. Subject is currently receiving a nonbiological investigational product or device or has received one within 4 weeks prior to Day 1.
4. Subject has had excessive sun exposure or has used tanning booths within 4 weeks prior to Day 1 or is not willing to minimize natural and artificial sunlight exposure during the trial. Use of sunscreen products (except on treated areas for subjects in Cohort 1) and protective apparel are recommended when sun exposure cannot be avoided.
5. Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
6. Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.

Exclusion criteria for Cohort 1 only (subjects with FFA):

7. History of other scalp/hair disease including discoid lupus erythematosus and central centrifugal cicatricial alopecia.

   Note: Subjects with lichen planopilaris/FFA overlap are not to be excluded.
8. Presence of active dermatologic condition that might interfere with FFA diagnosis and/or interfere with the trial assessments such as seborrheic dermatitis, psoriasis, or telogen effluvium.
9. Subject who has undergone scalp reduction surgery or hair transplantation.
10. Use of adhesive wigs during the trial.
11. Subject is known to have immune deficiency or is immunocompromised.
12. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
13. Subject had a major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the trial.
14. Subject has uncontrolled hypo- or hyperthyroidism or has both thyroid-stimulating hormone (TSH) and free T4 levels outside normal range at screening.
15. Subject has any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of trial results.
16. Subject has positive results for hepatitis B surface antigens (HBsAg), antibodies to hepatitis B core antigens (anti-HBc), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
17. Subject has used treatment with agents (including natural products or nutritional supplement such as Viviscal, Nutrafol, and/or biotin) that may affect hair regrowth in the last 4 weeks prior to Day 1.

Name of Sponsor/Company: LEO Pharma A/S	**Name of Investigational Product:** Delgocitinib cream 20 mg/g	**Name of Active Ingredient:** Delgocitinib

18. Subject has used intralesional scalp corticosteroids or platelet rich plasma injection in the last 4 weeks prior to Day 1.
19. Subject has used systemic treatment with immunosuppressive/modulating medication or medication that could affect FFA (eg, corticosteroids, methotrexate, minoxidil, hydroxychloroquine, retinoids, calcineurin inhibitor, tetracyclines, pioglitazone, spironolactone, or 5-α-reductase-inhibitors) within 4 weeks prior to Day 1.

    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.

    Note: Standard doses of systemic antihistamines are allowed.

    Note: Use of systemic treatment with minoxidil or spironolactone is allowed if used for at least 6 months prior to Day 1 and the subject agrees to continue using it on a stable dosing during the present study.
20. Subject has used any topical medicated treatment that could affect FFA within 2 weeks prior to Day 1, including, but not limited to, topical corticosteroids, calcineurin inhibitors, minoxidil, phosphodiesterase-4 (PDE-4) inhibitors.

    Note: Use of topical treatment with minoxidil is allowed if used for at least 6 months prior to Day 1 and the subject agrees to continue using it on a stable dosing during the present study.
21. Subject has received treatment with Janus kinase (JAK) inhibitors (systemic or topical) within 4 weeks prior to Day 1.
22. Subject has received any ultraviolet (UV)-B phototherapy (including tanning beds), excimer laser, or any other phototherapy within 4 weeks prior to Day 1.
23. Subject has had psoralen-UV-A (PUVA) treatment within 4 weeks prior to Day 1.
24. Subject has a known or suspected allergy to delgocitinib or any component of the IMP.
25. Subject has a history of an allergic reaction or significant sensitivity to hypoallergenic ink.
26. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.

<u>Exclusion criteria for Cohort 2 only (healthy subjects):</u>

27. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the trial assessments.
28. Subject has any clinically significant medical condition or physical/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of trial results.
29. Subject has a known history of chronic infectious disease (e.g., hepatitis B, hepatitis C, or HIV).
30. Subject has used a topical medicated treatment on the targeted skin sites within 2 weeks prior to skin samples collection (Day 1).

<u>Statistical methods:</u>

Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation (SD), median, minimum, maximum, first (Q1) and third (Q3) quartiles. Categorical variables will be presented in tables as frequencies and percentages.

Molecular Signature Changes Analyses:

A Mixed Effect Model Repeated Measurement (MMRM) will be used to detect any overall differences in the treatment effect at Week 12 compared to baseline in the molecular measurements. This formulation

Name of Sponsor/Company: LEO Pharma A/S	**Name of Investigational Product:** Delgocitinib cream 20 mg/g	**Name of Active Ingredient:** Delgocitinib

intrinsically models the within patient correlation structure as in the case of a paired t-test. This approach introduces less bias than restricting the analysis for those patients who completed the trial. Time points (baseline, Week 12), treatment group (active, vehicle, and healthy), and tissue (lesional and non-lesional) will be considered as fixed factors, while participant ID will be included as random factor.

Safety Analyses:

Safety data will be summarized descriptively per cohort. No missing data will be imputed, and no inferential statistics are planned. For Cohort 1, the safety analysis will include reported AEs, including TEAEs, and other safety information (ie. clinical laboratory evaluations and vital signs). For Cohort 2, the safety analysis will include reported procedural complications.

Efficacy Analyses:

The comparison between the groups for the exploratory efficacy endpoints involving change from baseline will be done using a MMRM, where the absolute change from baseline will be the dependent variable; the treatment group, the visit, and an interaction term for the treatment-by-visit will be the fixed effects; and the baseline value will be the covariate**.**

The other efficacy endpoints involving proportions of pruritus NRS, burning sensation NRS, and pain NRS will be analyzed using a Chi-square test.

Sample Size Consideration:

From Del Duca et al. (2020) paper[1], the difference in log2-fold changes (SD*) between FFA patients and healthy controls are reported to 4.851 (4.411), 5.298 (5.512) and 4.559 (4.891) for CXCL9, CXCL10 and IFN-γ, respectively.

A sample 30 subjects are randomized in an equal manner (1:1) to delgocitinib cream 20 mg/g or vehicle cream. It is expected that a reduction of at least 90% from baseline to Week 12 for the delgocitinib cream 20 mg/g treated subjects compared to only 5% in the vehicle group, normalized to healthy controls, will be observed.

With the above assumptions, the trial should have at least 80% disjunctive power, i.e. a statistically significant difference (tested at 5% one-sided level in an independent two-sample t-test) can be shown with at least 80% probability, in at least one of the genes, assuming no correlation between the tests and same level of variation as reported in the Del Duca et al. (2020) paper[1].

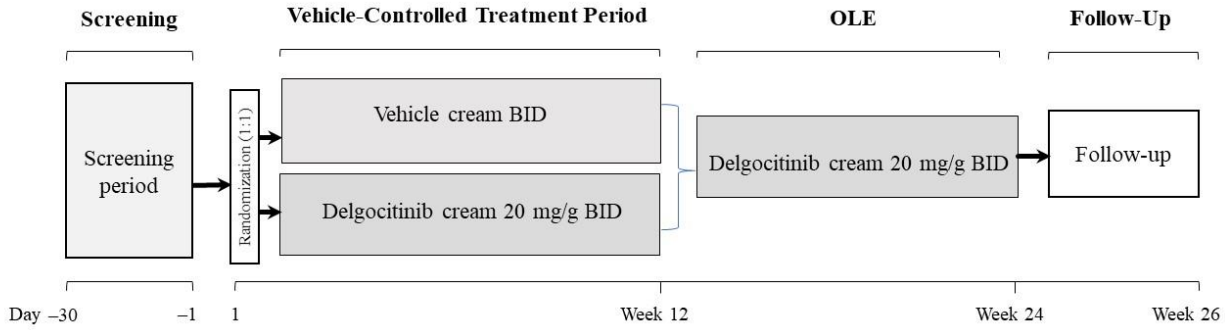
*Derived from the reported p-values coming from a t-test comparing lesional FFA biopsy data (N=12) to data from healthy controls (N=8).

1.2 Trial Diagram

Figure 1: Trial Diagram

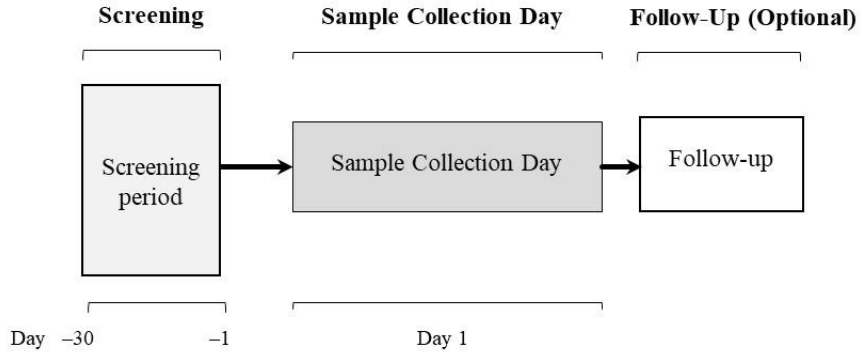
Cohort 1 and Cohort 2 can be conducted in parallel.

Cohort 1:



Abbreviations: BID, twice daily; OLE, open-label extension.

Cohort 2:



Notes: For Cohort 2 only, screening and skin samples collection on Day 1 can be performed on the same day at the investigator's discretion, if no medication washout is required and the lifestyle considerations are fulfilled. The optional follow-up period will occur 10 to 14 days after Day 1, to remove biopsy sutures, if needed.

1.3 Schedule of Events

The screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the ICF. No treatment or trial-related procedures will be initiated before the informed consent is signed. The Day 1 visit must be performed, at the latest, 30 days after the screening visit. For Cohort 2 only (healthy subjects), the sample collections on Day 1 can be performed on the same day as the screening visit or on separate visits as per the schedule of events, at the investigator's discretion.

The screening evaluation will be performed according to the inclusion and exclusion criteria. If the subject fulfills all inclusion criteria and no exclusion criteria, he or she may be included in the trial.

Table 1 and Table 2 provide a description of the procedures to be performed at each visit for Cohort 1 and Cohort 2, respectively.

Unless specified otherwise, the trial assessments scheduled during the trial visits must be performed before the IMP application for subjects in Cohort 1. If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:

- Patient-reported outcomes
- Investigator assessments
- Vital signs
- Medical photographs
- Collection of skin samples

Table 1: Schedule of Events for Cohort 1 (Subjects with FFA)

Trial Visits	Screening	Treatment Period							Follow-Up	ET
		Vehicle-Controlled				OLE				
		Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 26	-
	V1	V2	V3	V4	V5	V6	V7	V8	V9	-
Window (days)	-30 to -1	-	±2	±2	±2	±4	±4	±4	±4	-
Informed consent	X									
Demographics	X									
Medical and surgical history	X	X								
Inclusion-exclusion criteria	X	X								
Pregnancy test[a]	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests (biochemistry and hematology)	X	X	X	X	X	X	X	X		X
TSH and reflex free T4	X									
Serology (HBV [HBsAg, anti-HBc], HCV, HIV)	X									
Electrocardiogram	X									
Complete Physical examination	X				X			X	X	X
Brief Physical examination		X	X	X		X	X			
Vital signs[b]	X	X	X	X	X	X	X	X	X	X
Identification of a lesional target area on the scalp and of a non lesional area (eg. occipital scalp)[c]	X	X								

Trial Visits	**Screening**	**Treatment Period**							**Follow-Up**	**ET**
		Vehicle-Controlled				**OLE**				
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26**	**-**
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**-**
Window (days)	-30 to -1	-	±2	±2	±2	±4	±4	±4	±4	-
Perifollicular erythema and scale evaluation of the lesional target area	X	X	X	X	X	X	X	X		X
Pruritus NRS[d]	X	X	X	X	X	X	X	X		X
Burning Sensation NRS[d]	X	X	X	X	X	X	X	X		X
Pain NRS[d]	X	X	X	X	X	X	X	X		X
LPPAI		X	X	X	X	X	X	X		X
FFASS		X	X	X	X	X	X	X		X
Hair counts/Trichoscopy		X			X			X		X
Hair line measurements[e]		X			X			X		X
Medical photographs[f]		X			X			X		X
Randomization		X								
IMP application at site		X	X	X	X	X	X			
IMP application BID[g]		X----------X								
IMP distribution		X	X	X	X	X	X			
IMP collection and/or accountability and/or compliance			X	X	X	X	X	X		X
Subject diary distribution/collection/review	X	X	X	X	X	X	X	X		X
Local tolerability assessments[h]		X	X	X	X	X	X	X		X

Trial Visits	**Screening**	**Treatment Period**							**Follow-Up**	**ET**
		Vehicle-Controlled				**OLE**				
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26**	**-**
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**-**
Window (days)	-30 to -1	-	±2	±2	±2	±4	±4	±4	±4	-
Skin biopsies collection[i,j]		X			X					
Adhesive skin tape strip samples[k]		X			X					
Skin microbiome samples[l]		X			X					
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Adverse events collection	X	X	X	X	X	X	X	X	X	X

Abbreviations: anti-HBc, antibody to hepatitis B core antigen; BID, twice daily; ET, early termination; FFA, frontal fibrosing alopecia; FFASS, Frontal Fibrosing Alopecia Severity Score; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IMP, investigational medicinal product; LPPAI, lichen planopilaris activity index; NRS, Numerical Rating Scale; OLE, open-label extension; TSH, thyroid-stimulating hormone; V, visit.

[a] For female subjects of childbearing potential, serum pregnancy test at screening and urine pregnancy test at other specified visits.
[b] Including height and weight. Height will be measured only at screening.
[c] The lesional target area should be treated with the IMP and should be approximately 3 cm x 6 cm (or equivalent). However, a smaller lesional target area can be selected if tape stripping is performed from the same area where trichoscopy/hair counts is performed or if sample is collected adjacent/close to the lesional target area (refer to Section 8.3.2 for details). If needed, two small lesional target areas (totalling approximately the same size) could be selected to allow for skin samples collection.
[d] Subjects will complete their NRS at home on a daily basis starting approximately 7 days prior to Day 1 and up to Day 8. On Day 1, the NRS will be completed at the site prior to the first IMP application. After Day 8, the NRS will be completed at the site at the specified visits only.
[e] Hair line measurements of lateral canthus (right and left) to hairline, lower glabellar crease to hair line, top of frontalis muscle to hair line, and mid brow to hair line (right and left).
[f] Medical photographs of the target area and the entire scalp (including the frontal hair line and right and left hair line areas).
[g] The morning application will be on site on visit days. Other IMP applications will be done at home. The first application of the OLE (delgocitinib cream 20 mg/g) is on the morning of Week 12, after all efficacy assessments and skin sample collections are completed. The last application of the OLE is the evening prior to the Week 24 visit. No IMP application will be done on the day of the Week 24 visit.
[h] Local tolerability assessments will be done by subjects. On Day 1 and Week 12, the local tolerability assessment will be done approximately 30 minutes after the IMP application at the site, with a recall period of 30 minutes. At other visits, the subject's local tolerability assessment will be done before the IMP application with a recall period of 7 days (worst over the last 7 days).

Trial Visits	**Screening**	**Treatment Period**							**Follow-Up**	**ET**
		Vehicle-Controlled				**OLE**				
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26**	**-**
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**-**
Window (days)	-30 to -1	-	±2	±2	±2	±4	±4	±4	±4	-

[i] On Day 1, 2 skin biopsies (4-mm) will be collected prior to the first IMP application (1 from a lesional hair follicle within the target area and 1 from a non lesional hair follicle [eg, on the occipital scalp]). On Week 12, 1 skin biopsy (4-mm) will be collected from a hair follicle within the lesional target area (outside the scar of previous biopsies).

[j] Within 10 to 14 days after biopsy collection, suture may be removed, if needed. An additional visit(s) may be necessary for suture removal only, if suture removal is needed after Day 1 and/or Week 12.

[k] On Day 1, optional skin tape strips will be collected prior to the first IMP application from lesional skin and from non lesional skin (eg, on the occipital scalp). The lesional skin tape strip should ideally be collected from the target area but can also be collected adjacent/close to the target area, as long as it includes a portion of lesional skin and is treated with the IMP. On Week 12, skin strips will be collected at the same location of the lesional skin. Every effort should be made to collect tape strip samples in all subjects however, adhesive tape strip collection is optional and will be collected per investigator judgement (based on available skin area on the scalp).

[l] On Day 1, skin swab for microbiome analysis will be collected prior to the first IMP application (1 from the target area [lesional skin] and 1 from an uninvolved occipital scalp area). On Week 12, skin microbiome will be collected at the same location of the lesional skin of the target area.

Table 2: Schedule of Events for Cohort 2 (Healthy Subjects)

Trial Visits	Screening	Sample Collection Day	Follow-Up (Optional)
	V1	V2	V3
Window (days)	-30 to -1	-	10 to 14 days after Day 1
Informed consent	X		
Demographics	X		
Medical and surgical history	X	X	
Inclusion-exclusion criteria	X	X	
Brief physical examination	X	X	
Vital signs[a]	X	X	
Skin biopsies collection[b]		X	
Suture removal (if applicable)			X
Adhesive skin tape strip samples[c]		X	
Skin microbiome samples[d]		X	
Concomitant medication	X	X	X
Procedural complications evaluation	X	X	X

Abbreviation: V, visit.
Note: Screening and Day 1 can be performed on the same day (if subjects do not have a washout period for any of the medications or procedures listed in the exclusion criterion or lifestyle considerations) and the scheduled assessments on these two days can be completed only once in this case.
[a] Including height and weight. Height will be measured only at screening.
[b] Two skin biopsies (4-mm) that include hair follicles will be collected on healthy skin at similar matched areas of subjects with FFA (ie., 1 from frontal area and 1 from occipital scalp area).
[c] Skin tape strips will be collected on non-hair bearing healthy skin at a similar matched area of subjects with FFA (ie, on the forehead, as close as possible to the frontal scalp area).
[d] Two skin swab samples for microbiome analysis will be collected on healthy skin at similar matched areas of subjects with FFA (ie, 1 on frontal scalp area and 1 from occipital scalp area).

2 INTRODUCTION

2.1 Background

2.1.1 Frontal Fibrosing Alopecia

Frontal fibrosing alopecia (FFA) was first described in 1994 and is a type of primary lymphocytic cicatricial alopecia that is often considered a clinical variant of lichen planopilaris (LPP) due to their shared histopathologic features.[2] This variant of LPP is most commonly found in postmenopausal women and is increasing in prevalence.[3] FFA is characterized by the recession of the frontal, temporal, or frontotemporal hairline; the clinical pattern is distinct and usually includes eyebrow hair loss, as well as other associated symptoms. Pruritus, facial papules, eyelash loss, body hair involvement, and trichodynia may also occur in addition to the frontotemporal recession and eyebrow loss classically seen.[2]

Early diagnosis and prompt treatment are critical as FFA is a progressive disorder that can result in permanent hair loss. However, even with aggressive therapy, FFA may progress. There are a limited number of published guidelines for the treatment of FFA and there is no consensus or standard treatment regimen for FFA.[2] Intralesional corticosteroids may achieve some disease stabilization, with associated adverse effects such as pain and skin atrophy, and topical corticosteroids are often not effective.[1] In addition, no therapeutic interventions selectively target cellular or molecular key elements of FFA pathogenesis.[4]

The etiology and pathogenesis of FFA are not completely understood and remain areas of active investigation. The inflammatory cell infiltrate surrounding lesional hair follicles, namely around the bulge and infundibulum, is characterized by an increase in CD8+ GranzymeB+ cytotoxic T cells and plasmacytoid dendritic cells (pDC), with elevated levels of the chemokine receptor CXCR3 expression.[4] The available evidence suggests a key role for interferon (IFN)-γ in inducing hair follicule immune privilege (HFIP) bulge collapse and subsequent immune-mediated epithelial hair follicle stem cells (eHFSC) destruction observed in FFA.[4] Therapeutically, bulge immune privilege protection/restoration or neutralizing IFN-γ may help to better manage this highly treatment-resistant cicatricial alopecia.

2.1.2 Delgocitinib

Delgocitinib is a novel pan-Janus kinase (JAK) inhibitor. After a cytokine binds to its receptor, the JAK family is activated intracellularly, and promotes growth and activation of a variety of cells (eg, lymphocytes) via phosphorylation of the downstream substrate signal transducer and activator of transcription (STAT). The JAK family is essential for the physiological activity of cytokines and plays a critical role in the pathogenesis of diseases with an immunoinflammatory component.[5]

The JAK-STAT pathway is a promising target for the treatment of disorders with an immunoinflammatory component. Several JAK inhibitors (such as ruxolitinib, baricitinib, and tofacitinib) are in clinical development or are already approved for oral or topical treatment of various chronic inflammatory conditions. Delgocitinib ointment (that was developed by Japan Tobacco In. [JT]) has been approved for topical treatment of children aged 2 years and older and

adults with atopic dermatitis (AD) in Japan and delgocitinib cream has shown promising efficacy in inflammatory skin diseases such as chronic hand eczema and AD.[5]

Based on the nonclinical and clinical data currently available, delgocitinib has the potential to become a novel local-acting, selective immunosuppressive agent suitable for the topical treatment of inflammatory dermatological diseases such as FFA.[5]

2.1.3 Trial Rationale

FFA demonstrated significant upregulation of T helper 1/IFN (IFN-γ, CXCL9/CXCL10), the JAK-STAT pathway (STAT1, JAK3) and fibrosis-related products (vimentin, fibronectin).[1] The increased expression of IFN-γ-inducible chemokines (CXCL9, CXC10, and CXC11) and cognate receptor 3 (CXCR3) in lesional FFA bulge epithelium suggest that the CXCL9/10/11-CXCR3 signaling system plays a major role in attracting the inflammatory cell infiltrate in FFA. Interfering with the JAK-STAT signaling pathway may be a novel approach to suppress aberrant immune responses in patients with FFA.[6]

It is hypothesized that delgocitinib cream 20 mg/g will reduce INF-γ driven inflammation in subjects with FFA. In the present trial, the molecular signature changes following topical application of delgocitinib cream 20 mg/g in subjects with FFA will be evaluated. The safety and preliminary efficacy of delgocitinib cream in subjects with FFA will also be evaluated.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

A total of 15 clinical trials, 1 with oral delgocitinib (sponsored by JT), 11 with delgocitinib ointment (7 sponsored by JT and 4 sponsored by LEO Pharma A/S), and 3 with delgocitinib cream (sponsored by LEO Pharma A/S), have been completed and 2 clinical trials with delgocitinib cream are currently ongoing (sponsored by LEO Pharma A/S). In total, 54 subjects were dosed orally with delgocitinib (at doses between 1 and 100 mg) and 1635 subjects were exposed topically to delgocitinib ointment (1165 subjects at concentrations between 0.3 and 30 mg/g) or delgocitinib cream (470 subjects at concentrations between 1 and 20 mg/g).

Delgocitinib ointment and delgocitinib cream were well tolerated in the conducted clinical trials and systemic exposure to delgocitinib has been low. No clinical indication of any phototoxic potential was observed for delgocitinib cream when single occlusive application of delgocitinib was followed by light exposure in healthy subjects. Potential risks to humans that could arise from use of delgocitinib cream are local skin infection, and acneiform eruptions, which have been reported in clinical trials with delgocitinib ointment. Only few serious adverse events (SAEs) were reported in the completed clinical trials. Except for one, all SAEs were considered not related to treatment. There was no pattern in the reported preferred terms (PT). The one related SAE was an event of *Kaposi's varicelliform eruption* reported in a JT trial with delgocitinib ointment in Japanese subjects. The subject experiencing this event was hospitalized, and the event was resolved.

Generally, no clinically significant changes in laboratory test values, in systolic blood pressure, diastolic blood pressure, pulse rate, or body temperature were observed in subjects exposed to delgocitinib cream. Lymphocytopenia was observed in oral nonclinical toxicity studies and is considered a potential clinical consequence of systemic levels of delgocitinib. Lymphocytopenia is therefore considered an important potential risk for delgocitinib cream.

Further information related to nonclinical and clinical studies is available in the Investigator Brochure (IB).[5]

2.2.2 Known Potential Benefits

For Cohort 1, it is anticipated that subjects randomized to the active investigational medicinal product (IMP) during the vehicle--controlled treatment period and all subjects continuing into the OLE will see an improvement or a stabilization in their FFA condition as a result of participating in this Phase 2a trial.

For Cohort 2, there are no anticipated benefits for subjects participating in the trial, other than the benefit of medical evaluation at screening and throughout the trial.

Participation in this trial may help generate future benefit for larger groups of patients with FFA.

2.2.3 Assessment of Risks and Benefits

All previous data demonstrated in nonclinical and clinical trials are considered sufficient to expect a positive benefit/risk ratio for the treatment of FFA with delgocitinib cream 20 mg/g, and therefore to initiate this trial.

The risks to subjects in this trial will be minimized by compliance with the eligibility criteria, proper trial design, and close monitoring.

2.2.4 COVID-19 Pandemic

Initiating and conducting clinical trials during Coronavirus Disease 2019 (COVID-19) pandemic, presents numerous challenges. Control measures in place in different regions may impact the ability to adhere to some of the trial procedures described in this protocol. Due to challenges that include but are not limited to participant preferences, site closures, travel restrictions, and quarantines, some modifications to trial conduct during the COVID-19 pandemic may be necessary to ensure trial continuity and safety of the participants and trial staff. Adequate benefit/risk analyses should be applied relative to the completion of study procedures. Recognizing the flexibility required to manage the impact of the pandemic on this clinical trial, additional details may be added to study manual(s) and communicated to the site, as needed.

Taking into account the modifications to trial conduct that could occur to minimize risk related to COVID-19 in this trial, the potential risks to participate in this trial during the pandemic are justified by the anticipated benefits that may be afforded to subjects with FFA.

In addition, it is not believed that treatment with delgocitinib cream will put subjects at an increased risk for viral infections, including SARS-CoV-2. Vaccination for COVID-19 will be

allowed during the study, if needed, without changes in currently planned trial procedures and IMP applications.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To assess molecular signature changes following topical application of delgocitinib cream 20 mg/g in subjects with FFA	Primary endpoint: • Change in expression of CXCL9, CXCL10, and IFN-γ from baseline to Week 12.
Secondary	
To evaluate the safety and tolerability of delgocitinib cream 20 mg/g following topical application in subjects with FFA during the vehicle-controlled treatment period.	Safety endpoint during the vehicle-controlled treatment period: • Number of TEAEs from baseline to Week 12.
Exploratory	
To evaluate the safety and tolerability of delgocitinib cream 20 mg/g during the OLE.	Exploratory safety endpoint: • Number of TEAEs during the OLE (up to Week 26)
To evaluate the preliminary efficacy of delgocitinib cream 20 mg/g following topical application in subjects with FFA.	Exploratory efficacy endpoints during the vehicle-controlled treatment period: • Change in LPPAI score from baseline to Weeks 4, 8, and 12. • Change in FFASS score from baseline to Weeks 4, 8, and 12. • Change in target area perifollicular erythema score from baseline to Weeks 4, 8, and 12. • Change in target area perifollicular scale score from baseline to Weeks 4, 8, and 12. • Change in pruritus NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12. • Change in burning sensation NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12. • Change in pain NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12. • Proportion of subjects with a 3-point reduction* in pruritus NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12. • Proportion of subjects with a 4-point reduction* in pruritus NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12.

OBJECTIVES	ENDPOINTS
	• Proportion of subjects with a 3-point reduction* in burning sensation NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12. • Proportion of subjects with a 4-point reduction* in burning sensation NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12. • Proportion of subjects with a 3-point reduction* in pain NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12. • Proportion of subjects with a 4-point reduction* in pain NRS score from baseline to Days 2, 3, 4, 5, 6, 7, 8, and Weeks 4, 8, and 12. • Change in target area hair counts/trichoscopy via fotofinder trichovision from baseline to Week 12.
	Exploratory efficacy endpoints during the OLE:
	• These efficacy outcomes will be measured at scheduled visits after Week 12: LPPAI, FFASS, target area perifollicular scale score, target area perifollicular erythema score, pruritus NRS, burning sensation NRS, pain NRS, and target area hair counts/trichoscopy via fotofinder trichovision.

Abbreviations: CXCL9, chemokine (C-X-C motif) ligand 9; 10, chemokine (C-X-C motif) ligand 10; FFA, frontal fibrosing alopecia; FFASS, Frontal Fibrosing Alopecia Severity Score; INF, interferon, LPPAI, Lichen Planopilaris Activity Index; NRS, Numerical Rating Scale; TEAE, treatment-emergent adverse event.

* Only subjects with a baseline NRS score ≥3 will be included in the respective endpoints on proportion of subjects with a 3-point reduction. Only subjects with a baseline NRS score ≥4 will be included in the respective endpoints on proportion of subjects with a 4-point reduction.

4 TRIAL DESIGN

4.1 Overall Design

A Phase 2a, randomized, double-blind, vehicle-controlled, single-site, exploratory trial of delgocitinib cream 20 mg/g in subjects with FFA.

The trial will consist of 2 cohorts: Cohort 1 will include approximately 30 subjects with FFA and Cohort 2 will include approximately 5 healthy postmenopausal female subjects. Both cohorts can be conducted in parallel.

Cohort 1:

All subjects will read and sign an informed consent form (ICF) prior to any trial-related activities being performed. Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be randomized into the trial. After a screening period of no more than 30 days (from Day -30 to Day -1), eligible subjects will be randomized (1:1) on Day 1 to apply delgocitinib cream 20 mg/g or vehicle cream BID for 12 weeks during the vehicle-controlled treatment period. All subjects who complete the vehicle-controlled treatment period will then continue into the OLE and apply delgocitinib cream 20 mg/g BID for 12 weeks. The OLE period will be followed by a 2-week safety follow-up period. For scheduled trial visits, subjects will come to the site on 9 occasions: screening, Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, and Week 26/early termination (ET).

On Day 1, a lesional target area on the scalp (eg, frontal, periauricular, or temporal area) that be treated with the IMP will be identified. To allow for the hair count/trichoscopy assessment and all samples collection (ie, skin biopsies, tape stripping, and skin swabs) the lesional target area should be approximately 3 cm x 6 cm (or equivalent). However, as tape strips can be collected from the same area where trichoscopy/hair counts is performed or can be collected adjacent/close to the lesional target area (refer to Section 8.3.2 for details), a smaller lesional target area may be acceptable. If needed, two small target areas (totalling approximately the same size) could also be selected to allow for skin samples collection and hair count/trichoscopy assessment. If two lesional target areas are selected, they should be of similar severity.

The following skin samples will be collected during the trial to assess molecular signature changes:

- Skin biopsies for transcriptomic and immunohistochemistry (IHC) analyses (n=3):
    - *Day 1:* 2 skin biopsies (4-mm) will be collected prior to the first IMP application (1 from a lesional hair follicle within the target area and 1 from a non lesional hair follicle [eg, on the occipital scalp]).
    - *Week 12:* 1 skin biopsy (4-mm) will be collected from a hair follicle within the lesional target area (outside the scar of previous biopsies).
- Skin swabs for microbiome analysis (n=3):
    - *Day 1*: 2 skin microbiome samples will be collected prior to the first IMP application (1 from the target area [lesional skin] and 1 from an uninvolved occipital scalp area).

  - *Week 12*: 1 skin microbiome sample will be collected at the same location of the lesional skin of the target area.

- Adhesive tape strips samples for transcriptomic analysis (n=3):
  - *Day 1*: skin tape strips will be collected prior to the first IMP application from lesional skin and from a nonlesional skin (eg, on the occipital scalp).
  - *Week 12*: skin tape strips will be collected at the same location of the lesional skin.

  Note: Every effort should be made to collect tape strip samples in all subjects however, adhesive tape strip collection is optional and will be collected per investigator's judgement (based on available skin area on the scalp).

Safety will be assessed by collecting adverse events (AEs), recording vital signs, performing complete and brief physical examinations, and evaluating clinical laboratory results and local tolerability assessments (LTA).

Efficacy will be assessed using LPPAI, FFASS, evaluation of the perifollicular erythema and perifollicular scale, pruritus NRS, burning sensation NRS, pain NRS, and hair counts/trichoscopy (eg, number of hairs, hair diameter, and hair density). Hair line measurements (ie, lateral canthus [right and left] to hairline, lower glabellar crease to hair line, top of frontalis muscle to hair line, and mid brow to hair line [right and left]) will also be done.

Medical photographs of the lesional target area and the entire scalp (including the frontal hair line and right and left hair line areas) will be taken with the fotofinder device during the trial.

Cohort 2:

All subjects will read and sign an ICF prior to any trial-related activities being performed. Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be accepted into the trial. After a screening period of no more than 30 days (from Day -30 to Day -1), eligible subjects will be asked to come at the site for skin samples collection. Screening and skin samples collection on Day 1 can be performed on the same day (if subjects do not have a washout period) or on two separate visits, at the investigator's discretion. No investigational product will be administered in Cohort 2. For scheduled trial visits, subjects will come to the site on up to 3 occasions: screening, Day 1, and optional follow-up visit.

The following skin samples will be collected:

- Skin biopsies (n=2):
  - *Day 1:* 2 skin biopsies (4-mm) that include hair follicles will be collected on healthy skin at similar matched areas of subjects with FFA (ie, 1 from frontal scalp area and 1 from occipital scalp area)
- Adhesive tape strips (n=1):
  - *Day 1*: skin tape strips will be collected on non-hair bearing healthy skin at a similar matched area of subjects with FFA (ie, on the forehead, as close as possible to the frontal scalp area).

- Skin swabs for microbiome analysis (n=2):
    - *Day 1*: 2 skin microbiome samples will be collected on healthy skin at similar matched areas of subjects with FFA (ie, 1 from frontal scalp area and 1 from occipital scalp area).

For Cohort 2 only, safety will be assessed by review of any procedural complications and changes in health observed after skin samples collection.

No interim analysis is planned in this trial.

4.2 Scientific Rationale for Trial Design

This is an exploratory trial to interrogate the effect of delgocitinib cream 20 mg/g on the molecular signature of active FFA. Frontal fibrosing alopecia demonstrated significant upregulation of T helper 1/IFN (IFN-γ, CXCL9/CXCL10), the JAK-STAT pathway (STAT1, JAK3) and fibrosis-related products (vimentin, fibronectin). Delgocitinib is a novel pan- JAK inhibitor. It is hypothesized that delgocitinib cream 20 mg/g will reduce INF-γ driven inflammation in subjects with FFA. The proposed design is considered appropriate for assessing the molecular signature changes, the safety, as well as preliminary efficacy of delgocitinib cream 20 mg/g in subjects with FFA.

In this Phase 2a trial, the vehicle-controlled treatment period will be randomized to ensure random allocation of subjects to treatment arms to reduce bias. Because efficacy assessments of FFA have a high degree of subjectivity, the trial will be double-blinded. The highest degree of patient and assessor blinding should be sought to achieve credible inference. It is also important to have a vehicle control in the Phase 2a trial to control for confounding factors, such as potential investigator bias, and to ensure that the statistical procedures can be appropriately applied. After completion of the vehicle-controlled treatment period, all subjects will have the opportunity to continue into the OLE and to receive the active drug for a period of 12 weeks.

Inclusion of 5 healthy postmenopausal female subjects to collect skin samples will allow comparison of the molecular and cellular fingerprint to that of subjects with FFA.

4.3 Justification for Dose

The justification for the delgocitinib dose is based on the findings from the Phase 2b trial in subjects with AD. Delgocitinib cream was tested at 4 different strengths (1, 3, 8, and 20 mg/g) BID for up to 8 weeks in subjects with AD. A statistically significant dose-response was established for the primary endpoint (change in Eczema Area and Severity Index [EASI] from baseline to Week 8), and the secondary endpoints (Validated Investigator Global Assessment for Atopic Dermatitis treatment success [vIGA-AD TS] at Week 8 and EASI75 [a 75% reduction in EASI score] at Week 8). The highest treatment effect (compared to cream vehicle) was seen with delgocitinib cream 20 mg/g.

4.4 End of Trial Definition

A subject is considered to have completed the trial if he or she has completed all phases of the trial, including the last visit or the last scheduled procedure shown in the Schedule of Events, Table 1 (for Cohort 1) and Table 2 (for Cohort 2).

The end of the trial is defined as completion of the last visit or procedure shown in the schedule of event for the last enrolled subject in Cohort 1 and Cohort 2.

5 TRIAL POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this trial, a subject must meet all of the following criteria, either at the screening and Day 1 visits or only at one of the specified visits (screening or Day 1) as noted in the criterion:

Inclusion criteria for all subjects:

1. Subject is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any trial-related procedures.
2. Subjects must be willing to comply with all trial procedures and must be available for the duration of the trial.

Inclusion criteria for Cohort 1 only (subjects with FFA):

3. Male or female subject aged 18 years of age or older at the time of consent.
4. Female subject of childbearing potential has had a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
5. Subject has clinically confirmed diagnosis of FFA based on investigator's judgment.
6. Subject has a target area with a perifollicular erythema score ≥ 2 and a perifollicular scale score ≥ 2 at Screening and Day 1.
7. For subject who uses make-up, moisturizers, creams, lotions, cleansers, and/or sunscreens on the face, subject has used the same product brands/types for a minimum period of 4 weeks prior to Day 1, agrees not to change brand/type or frequency of use throughout the trial, agrees not to apply those products on the treated area during the trial, and agrees not to use make-up, moisturizers, creams, lotions, cleansers, and/or sunscreens on the face on the clinic visit days before the visit.
8. Subject is willing to maintain a consistent hair style and hair style regimen, including shampoo and hair products (including hair dye, process, and timing to hair appointments), and to refrain from weaves or extensions throughout the course of the trial and for 4 weeks prior to Day 1.

   Note: Hair dying and shaving of scalp is allowed during the trial but not within 48 hours prior to a trial visit
9. For female subject of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use an effective contraceptive method from at least 4 weeks prior to Day 1 until at least 4 weeks after the last IMP application. Effective contraceptive methods include hormonal contraceptives (eg, combined oral contraceptive, progesterone-only hormonal contraception [associated with or without inhibition of ovulation as the primary mode of action], patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s) (provided his vasectomy was performed ≥4 months prior to Screening), tubal ligation or a barrier method of contraception (eg, male condom, female condom, cervical cap, diaphragm, contraceptive sponge) in conjunction with spermicide.

   Note: Subjects must have been on a stable dose of hormonal contraceptives for at least 4 weeks before Day 1.

Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the trial. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable.

Note: A female subject of nonchildbearing potential is defined as follows:

- Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
- Female subject who has had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause

Inclusion criteria for Cohort 2 only (healthy subjects):

10. Female subject aged 45 years of age or older at the time of consent.
11. Female is postmenopausal as defined below:
    - Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
    - Female subject who has had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause.
12. Subject is in good general health, according to the investigator's judgment based on vital signs, medical history, and brief physical examination.

5.2 Exclusion Criteria

A subject who meets any of the following criteria at the screening and/or Day 1 visits, as applicable, will be excluded from participation in this trial:

Exclusion criteria for all subjects:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the trial.
2. Subject has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
3. Subject is currently receiving a nonbiological investigational product or device or has received one within 4 weeks prior to Day 1.
4. Subject has had excessive sun exposure or has used tanning booths within 4 weeks prior to Day 1 or is not willing to minimize natural and artificial sunlight exposure during the trial. Use of sunscreen products (except on treated areas for subjects in Cohort 1) and protective apparel are recommended when sun exposure cannot be avoided.
5. Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
6. Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.

Exclusion criteria for Cohort 1 only (subjects with FFA):

7. History of other scalp/hair disease including discoid lupus erythematosus and central centrifugal cicatricial alopecia.

   Note: Subjects with lichen planopilaris/FFA overlap are not to be excluded.
8. Presence of active dermatologic condition that might interfere with FFA diagnosis and/or interfere with the trial assessments such as seborrheic dermatitis, psoriasis, or telogen effluvium.
9. Subject who has undergone scalp reduction surgery or hair transplantation.
10. Use of adhesive wigs during the trial.
11. Subject is known to have immune deficiency or is immunocompromised.
12. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
13. Subject had a major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the trial.
14. Subject has uncontrolled hypo- or hyperthyroidism or has both thyroid-stimulating hormone (TSH) and free T4 levels outside normal range at screening.
15. Subject has any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of trial results.
16. Subject has positive results for hepatitis B surface antigens (HBsAg), antibodies to hepatitis B core antigens (anti-HBc), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
17. Subject has used treatment with agents (including natural products or nutritional supplement such as Viviscal, Nutrafol, and/or biotin) that may affect hair regrowth in the last 4 weeks prior to Day 1.
18. Subject has used intralesional scalp corticosteroids or platelet rich plasma injection in the last 4 weeks prior to Day 1.
19. Subject has used systemic treatment with immunosuppressive/modulating medication or medication that could affect FFA (eg, corticosteroids, methotrexate, minoxidil, hydroxychloroquine, retinoids, calcineurin inhibitor, tetracyclines, pioglitazone, spironolactone, or 5-α-reductase-inhibitors) within 4 weeks prior to Day 1.

    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.

    Note: Standard doses of systemic antihistamines are allowed.

    Note: Use of systemic treatment with minoxidil or spironolactone is allowed if used for at least 6 months prior to Day 1 and the subject agrees to continue using it on a stable dosing during the present study.
20. Subject has used any topical medicated treatment that could affect FFA within 2 weeks prior to Day 1, including, but not limited to, topical corticosteroids, calcineurin inhibitors, minoxidil, phosphodiesterase-4 (PDE-4) inhibitors.

    Note: Use of topical treatment with minoxidil is allowed if used for at least 6 months prior to Day 1 and the subject agrees to continue using it on a stable dosing during the present study.

21. Subject has received treatment with JAK inhibitors (systemic or topical) within 4 weeks prior to Day 1.
22. Subject has received any ultraviolet (UV)-B phototherapy (including tanning beds), excimer laser, or any other phototherapy within 4 weeks prior to Day 1.
23. Subject has had psoralen-UV-A (PUVA) treatment within 4 weeks prior to Day 1.
24. Subject has a known or suspected allergy to delgocitinib or any component of the investigational product.
25. Subject has a history of an allergic reaction or significant sensitivity to hypoallergenic ink.
26. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.

Exclusion criteria for Cohort 2 only (healthy subjects):

27. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the trial assessments.
28. Subject has any clinically significant medical condition or physical/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of trial results.
29. Subject has a known history of chronic infectious disease (e.g., hepatitis B, hepatitis C, or HIV).
30. Subject has used a topical medicated treatment on the targeted skin sites within 2 weeks prior to skin samples collection (Day 1).

5.3 Lifestyle Considerations

Cohort 1:

For subject who uses make-up, moisturizers, creams, lotions, cleansers, and/or sunscreens on the face, the same product brands/types should be used for a minimum period of 4 weeks prior to Day 1. Subject should continue to use the same brand/type or frequency of use throughout the trial, but should not apply those products on the treated area during the trial. On clinic visit days, subjects should not use make-up, moisturizers, creams, lotions, cleansers, and/or sunscreens on the face on the clinic visit days before the visit. In addition, for the subjects who are on stable dose of topical minoxidil for at least 6 months prior to Day 1 and continue using it during the study, they should be instructed to not apply it on the areas where skin samples will be collected on the visit days before the visit.

Subject should maintain a consistent hair style and hair style regimen, including shampoo and hair products (including hair dye, process, and timing to hair appointments), and should refrain from weaves or extensions throughout the course of the trial and for 4 weeks prior to Day 1. Hair dying and shaving of scalp is allowed during the trial but not within 48 hours prior to a trial visit. Subjects will be informed to wash their scalp/hair approximately 48 hours prior the visits on Day 1 and Week 12 and then to keep their hair free of products until these visits (ie, the visits where skin microbiome will be collected). For other visits (Weeks 4, 8, and 24 [or ET, as applicable]), subjects will be informed that they should not apply hair products before the visits.

The IMP should be applied after hair washing if this coincides with time for IMP application. Subjects should abstain from wetting the hair and eyebrows (if eyebrows are treated) within 2 hours following IMP application. Subjects should also wait at least 30 minutes after IMP application to wear protective apparel (eg, hat) or non-adhesive hair piece/wig that cover treated areas.

Subjects should abstain from physical activity that can cause significant sweating within 2 hours following IMP application.

Subjects should avoid eye contact with the IMPs.

Cohort 2:

On the Day 1 visit, subjects should not use make-up, moisturizers, creams, lotions, cleansers, and/or sunscreens on the face before the visit.

Subjects will be informed to wash their scalp/hair approximately 48 hours prior to the Day 1 visit and then to keep their hair free of products until the visit.

5.4 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical trial but are not subsequently randomly assigned to the IMP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once, if deemed acceptable by the investigator. Rescreened subjects should be assigned a different subject number than the initial screening. All procedures planned at the screening visit, including signature of a new consent form, will be performed.

6 TREATMENT

6.1 Trial Treatment Administered

No IMP will be administered in Cohort 2. For Cohort 1, the vehicle-controlled treatment period involves a comparison of delgocitinib cream 20 mg/g administered topically BID with a vehicle (delgocitinib cream vehicle). During the OLE, all subjects will apply delgocitinib cream 20 mg/g BID. All IMPs will be provided by the sponsor.

On Day 1, trial staff will instruct subjects on proper application of IMP. On Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20, the morning application of the IMP will be at the site under the supervision of trial staff. Other IMP applications will be self-administered by the subject at home. The last IMP application will be the evening prior to the Week 24 visit. No IMP application will be done on the day of the Week 24 visit. Typically, dosing will occur in the morning and evening, with approximately 12 hours between doses. The IMP will be applied to all affected areas on the face/scalp (ie, frontal scalp area, including the lesional target area, and eyebrows, if affected) as a thin layer. The original lesional area(s) identified at Day 1 and any new lesions (or increase in original lesional area) on the face/scalp must be treated until Week 24. The IMP should be applied after hair washing if this coincides with time for IMP application, and the hair should be dry before application. Subjects will be instructed to wash their hands with soap and water after IMP application and to wait at least 30 minutes before covering the treated areas.

Table 3: Trial Treatments

	Trial Treatments	
Product name	Delgocitinib	Delgocitinib Vehicle
Dosage form	Cream	Cream
Unit dose strength(s)/Dosage level(s)	20 mg/g	NA
Route of Administration	Topical	Topical
Dosing instructions	Applied BID to all affected areas on the face/scalp (ie, frontal scalp and eyebrows, if affected) for 12 weeks during the vehicle-controlled treatment period and for 12 weeks during the OLE.	Applied BID to all affected areas on the face/scalp (ie, frontal scalp and eyebrows, if affected) for 12 weeks during the vehicle-controlled treatment period.
Physical description	The drug product is a white to almost white cream	Vehicle is identical to the active cream.
Source of procurement	LEO Pharma A/S	LEO Pharma A/S

Abbreviations: BID, twice daily; NA, not applicable; OLE, open-label extension.

The contents of the label will be in accordance with all applicable regulatory requirements.

6.1.1 Treatment Interruption

In the event of an AE or laboratory abnormality, individual subject trial treatment may be temporarily interrupted based on the investigator's judgment and preferably following a discussion with the Medical Monitor.

Treatment may be resumed at the discretion of the principal investigator in consultation with the Medical Monitor.

The investigator may suspend trial treatment at any time, even without consultation with the Medical Monitor if the urgency of the situation requires immediate action and if it is determined to be in the subject's best interest. However, the Medical Monitor should be contacted as soon as possible for all cases of study drug interruption. Resumption of trial treatment after temporary discontinuation should always be discussed with the Medical Monitor.

The information pertaining to interruption of trial medication and the reasons for it must be recorded in the case report form.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Preparation/Storage/Handling

All IMPs must be stored in a secure environmentally controlled and monitored area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. The IMPs may only be supplied by authorized site staff and may only be given to subjects enrolled into the Cohort 1 of the trial.

Investigational medicinal products will be dispensed by the site to the subject in Cohort 1 at the visits specified in Table 1. Subjects are to return all IMPs (used and unused) to the site. The tubes will be weighed prior to dispensing and upon return, and the weight will be recorded in the source documents and electronic case report form (eCRF). Each subject will be instructed on the importance of returning IMP at the next trial visit and on taking the product as prescribed. If a subject does not return IMP, he or she will be instructed to return it as soon as possible.

More details on the application methods are described in the study manual.

6.2.2 Accountability

The investigator is responsible for maintaining accurate records of the IMP received initially and of the IMP dispensed/used. Any IMP accidentally or deliberately destroyed, or returned to the sponsor or designee will be accounted for. Any discrepancies between amounts dispensed and returned will be explained. At the conclusion of the trial, all used and unused investigational products and all medication containers will be returned or destroyed as per approved arrangements by the Sponsor.

All IMP accountability forms and treatment logs must be retained in the investigator's study files. Product inventory and accountability records will be maintained, as per ICH GCP. These records must be available for inspection at any time by the sponsor, its designees, or by regulatory agencies.

Further guidance and information for final disposition of IMPs are provided in the study manual.

6.3 Randomization

At the site, each screened subject will be assigned a subject identifier number during screening that will be used on all subject documentation. The subject identifier number will contain the site number (ie, 01) and the subject number and will be assigned in numerical order at the screening visit based on chronological order of screening dates (e.g., 01-010 for the 10th subject screened).

In Cohort 1, approximately 30 subjects will be randomized 1:1 to delgocitinib cream 20 mg/g or vehicle cream.

Further guidance and information about randomization assignment can be obtained in the study manual. The randomization number is to be recorded at the appropriate location in the source document and eCRF.

In Cohort 2, no randomization scheme will be used since no IMP will be applied.

6.3.1 Blinding

The vehicle-controlled treatment period of Cohort 1 will be double-blinded. At all times, treatment and randomization information will be kept confidential and will not be released to the investigator, the trial staff, the contract research organization (CRO), or the sponsor's trial team until after the conclusion of the trial.

While the safety of a subject always comes first, it is still important to carefully consider if unblinding is necessary to ensure a subject's safety. An emergency unblinding request can be made by the investigator, health care professionals who are not members of the trial staff, or authorized LEO Pharma personnel.

Provisions are in place for 24-hour emergency unblinding of individual subject treatment. If emergency unblinding is required, the investigator or delegated site staff can directly contact the emergency unblinding facility via a corresponding local emergency unblinding telephone number, that can be found in the Investigator Site File.

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

For a requester who is not a member of the site staff (eg, a physician in an emergency room), the local contact number for the emergency unblinding facility will be provided on the subject card to be used if the investigator or delegated site staff cannot be reached. Like the investigator or delegated site staff, the requester needs to provide the trial ID, the subject ID and the randomization code number to the emergency unblinding facility, that will immediately reveal the individual treatment allocation.

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

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

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

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

The subject for whom the blind has been broken will be discontinued from the trial and undergo the ET procedures. In cases where there are ethical reasons to have the subject remain in the trial, the investigator must obtain specific approval from the sponsor or its designee for the subject to continue in the trial. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded.

6.3.2 Trial Treatment Compliance

Trial treatment compliance will be monitored at each visit. Adherence to treatment will be assessed by direct questioning, review of the subject's diary, and by maintaining adequate IMP dispensing and return records. The date and time of each dose administered in the clinic will be recorded.

Subjects who are significantly noncompliant with treatment will be counseled and could be discontinued from the trial, at the discretion of the investigator, following consultation with the sponsor. A subject will also be considered significantly noncompliant if he or she intentionally or repeatedly takes more than the prescribed amount of IMP in the same time frame, as judged by the investigator.

6.4 Concomitant Therapy

All medications (including over-the-counter drugs, vitamins, herbal/natural products, and antacids) taken within 4 weeks prior to screening and throughout the trial must be recorded. In addition, the use of any prohibited medications must be recorded within the timeframe described in the exclusion criteria.

Medication entries may be captured as generic or trade names. Trade names should be used for combination drugs. Entries should include as much as possible of the following information: the dose, unit, frequency of administration, route of administration, start date, end date, and indication. If the medication is stopped or the dosage is changed, these details must be recorded.

6.4.1 Permitted Therapies

The following therapies are permitted:

- Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.

- Standard doses of systemic antihistamines are allowed.
- Use of systemic treatment with minoxidil or spironolactone is allowed if used for at least 6 months prior to Day 1 and the subject agrees to continue using it on a stable dosing during the present study.
- Use of topical treatment with minoxidil is allowed if used for at least 6 months prior to Day 1 and the subject agrees to continue using it on a stable dosing during the present study.
- Use of sunscreen products, except on treated areas, and protective apparel are permitted when sun exposure cannot be avoided. Of note, subjects should wait at least 30 minutes after IMP application to wear protective apparel (eg, hat) or non-adhesive hair piece/wig that cover treated areas.
- Vaccination for COVID-19 will be allowed during the trial.

6.4.2 Prohibited Therapies or Procedures

For subjects in Cohort 1, Table 4 lists prohibited medications that are not to be used from the defined washout periods before the first application of the IMP at the Day 1 visit through the last trial visit.

Subjects in Cohort 1 who start prohibited medications or therapies that could have an impact on FFA during the trial will be withdrawn from trial treatment. Subjects who start prohibited medications or therapies for other reasons during the trial may be withdrawn from trial treatment if an impact on efficacy assessment or safety of the subjects is expected. If in any doubt, investigators are advised to discuss medications with the medical monitor.

For subjects in Cohort 2, Table 5 lists prohibited medications that are not to be used from the defined washout periods before the Day 1 visit.

Table 4: Prohibited Therapies or Procedures for Cohort 1 (Subjects with FFA)

Prohibited medications, products, and procedures	Washout period prior to first dose (Day 1)
Scalp reduction surgery or hair transplantation	-
Any marketed or investigational biological agent	12 weeks or 5 half-lives (whichever is longer)
Major surgery	8 weeks
Nonbiological investigational product or device	4 weeks
Treatment with agents (including natural products or nutritional supplement such as Viviscal, Nutrafol, and/or biotin) that may affect hair regrowth	4 weeks
Intralesional scalp corticosteroids or platelet rich plasma injection	4 weeks

Prohibited medications, products, and procedures	Washout period prior to first dose (Day 1)
Systemic treatments with immunosuppressive/modulating medication or medication that could affect FFA (eg, corticosteroids, methotrexate, minoxidil, hydroxychloroquine, retinoids, calcineurin inhibitor, tetracyclines, pioglitazone, spironolactone, or 5-α-reductase inhibitors)	4 weeks
JAK inhibitors (systemic or topical)	4 weeks
PUVA treatment, UV-B phototherapy (including tanning beds) or excimer laser, any other phototherapy, excessive sun exposure or has used tanning booths	4 weeks
Topical medicated treatment that could affect FFA including, but not limited to topical corticosteroids, calcineurin inhibitors, minoxidil, PDE-4 inhibitors	2 weeks
Adhesive wigs	During the trial

Abbreviations: PDE-4, phosphodiesterase-4; FFA, frontal fibrosing alopecia; IMP, investigational medicinal product; JAK, Janus-Kinase; PUVA, psoralen-UV-A; UV, ultraviolet.

Table 5: Prohibited Therapies or Procedures for Cohort 2 (Healthy Subjects)

Prohibited medications, products, and procedures	Washout period prior to Day 1
Any marketed or investigational biological agent	12 weeks or 5 half-lives (whichever is longer)
Nonbiologial investigational product or device	4 weeks
Excessive sun exposure or has used tanning booths	4 weeks
Topical medicated treatment on the targeted skin sites	2 weeks

7 DISCONTINUATION AND LOST TO FOLLOW-UP

Subjects have the right to withdraw from the trial at any time for any reason without penalty. The investigator also has the right to withdraw subjects from the trial if he or she feels it is in the best interest of the subject or if the subject is uncooperative or noncompliant.

Should a subject decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible, particularly the examinations outlined in the ET visit (for Cohort 1 only).

The investigator or one of his or her staff members should contact the subject to determine as accurately as possible the primary reason for the withdrawal.

A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the trial. If the reason for removal of a subject is an AE (or a procedural complication for subjects in Cohort 2) or an abnormal laboratory test result, the principal specific event or test will be recorded.

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.1 Discontinuation

For Cohort 1, subjects who discontinue the trial after the first dose will be asked, if they agree, to come for a last assessment (ET visit). Subjects who are discontinued for safety reasons may be asked to come for additional follow-up visits, at the investigator's discretion, after the ET visit to ensure appropriate medical care and AEs follow-up.

Subjects who discontinue will not be replaced.

Reasons for discontinuation include the following:

- The investigator decides that the subject should be withdrawn. If this decision is made because of an SAE, the IMP is to be discontinued in that subject immediately and appropriate measures are to be taken. The investigator will notify the sponsor immediately.
- If an application site reaction occurs, the investigator should use his or her best medical judgement as to whether to continue subject's treatment.
- The attending physician requests that the subject be withdrawn from the trial.
- The subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the trial indication. In this case, discontinuation from the trial occurs immediately upon introduction of the new agent.
- The subject is lost to follow-up. In this case, a reasonable attempt to contact the subject and ascertain his or her status must be made, and these attempts must be documented.
- The subject becomes pregnant at any time during the trial.
- Other: the subject may withdraw from the trial for any other reason, including withdrawal of consent.
- The sponsor or regulatory authorities, for any reason, stop the trial. In this case, all subjects will be discontinued from the trial. The investigator will immediately, on discontinuance of the trial by the sponsor, in its entirety or at a clinical trial site, inform both the subjects and the research ethics board of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of subjects or other persons.

7.2 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the trial site staff.

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

- The site will attempt to contact the subject and reschedule the missed visit. The site will then counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or trial file.
- If all attempts to contact the subject fail, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

8 TRIAL ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments (Cohort 1 only)

Clinical evaluations of FFA will be performed by an experienced and qualified dermatologist (board certified or equivalent) or other suitably qualified and experienced designee. To assure consistency and reduce variability, the same assessor should perform all assessments on a given subject whenever possible.

8.1.1 Lichen Planopilaris Activity Index

The LPPAI will be assessed at the visits specified in Table 1. It is a quantitative measure of disease activity.[7] The LPPAI records symptoms (pruritus, pain, burning), signs (erythema, perifollicular erythema and scale), a measure of activity (the anagen pull test), and spreading of the condition. These subjective and objective measures have been assigned a numeric value to establish a disease activity score. The weights given to the symptoms (30%), signs (30%), anagen pull test (25%), and presence of spreading (15%) led to the equation: LPPAI (0-10) = (pruritus + pain + burning)/3 + (scalp erythema + perifollicular erythema + perifollicular scale)/3 + 2.5 (pull test) + 1.5 (spreading/2). Symptoms and signs are recorded on a 4-point scale: 0 = absent (negative), 1 = mild (+/-), 2 = moderate (+), and 3 = severe (++,+++). The anagen pull test, when present, is a reliable measure of local disease activity. It involves taking hold of 10 to 20 hairs between the thumb, second and third fingers at the scalp end of the hair shafts, and pulling firmly away from the scalp with a perpendicular force to slide the fingers to the ends of the hair. The result is recorded both as a binary value (0 for no anagen hairs and 1 for the presence of anagen hairs) and as anagen hairs/total hairs pulled. Last is the assessment of disease extension, recorded as 0 (no spreading) versus 1 (indeterminate) versus 2 (spreading). When the hair loss is difficult to judge, the issue of extension is recorded as indeterminate. A detailed procedure of LPPAI score calculation is provided in Appendix A.

8.1.2 Frontal Fibrosing Alopecia Severity Score

The FFASS will be assessed at the visits specified in Table 1. This index is based on the evaluation of the relevant clinical features in FFA.[8] Those features are the grade of frontal and temporal hairline recession (from 1 to 5), grade of eyebrow loss (none, partial, or total), severity and extent of perifollicular erythema and hyperkeratosis, and severity and frequency of pruritus and pain associated with FFA. The resulting severity scores range from 0 to 25, with higher scores indicating greater FFA severity. The clinical features included in the FFASS are grouped into two categories: extent of alopecia (up to 21 points) and inflammation (up to 4 points). A detailed procedure of FFASS score calculation is provided in Appendix B.

8.1.3 Perifollicular Erythema and Scale

The perifollicular erythema and perifollicular scale of the selected lesional target area will be assessed visually at the visits specified in Table 1. Each clinical finding (ie, perifollicular erythema and perifollicular scale) will be scored using the 4-point severity scale[7,9] presented in Table 6. To be eligible for this trial, subjects must have a lesional target area with a perifollicular erythema score ≥ 2 and a perifollicular scale score ≥ 2 at Screening and Day 1.

Table 6: Perifollicular Erythema and Perifollicular Scale Severity Scale

Score	Description
0	Absent/None
1	Mild
2	Moderate
3	Severe/Intense

8.1.4 Pruritus Numerical Rating Scale

The intensity of pruritus due to FFA will be recorded using a NRS.[10,11] It will be assessed daily starting approximately 7 days prior to Day 1 and up to Day 8. Thereafter, it will be assessed only at the visits specified in Table 1. This will be evaluated by asking subjects to assign a numerical score representing of the worst intensity over the last 24 hours of their symptoms on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms. The NRS of pruritus is presented in Appendix C.

8.1.5 Burning Sensation Numerical Rating Scale

The intensity of burning sensation due to FFA will be recorded using an NRS. It will be assessed daily starting approximately 7 days prior to Day 1 and up to Day 8. Thereafter, it will be assessed only at the visits specified in Table 1. This will be evaluated by asking subjects to assign a numerical score representing of the worst intensity over the last 24 hours of their symptoms on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms. The NRS of burning sensation is presented in Appendix C.

8.1.6 Pain Numerical Rating Scale

The intensity of pain due to FFA will be recorded using an NRS[12,13]. It will be assessed daily starting approximately 7 days prior to Day 1 and up to Day 8. Thereafter, it will be assessed only at the visits specified in Table 1. This will be evaluated by asking subjects to assign a numerical score representing of the worst intensity over the last 24 hours of their symptoms on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms. The NRS of pain is presented in Appendix C.

8.1.7 Hair Counts/Trichoscopy

Hair counts/trichoscopy will be performed at the visits specified in Table 1. Trichoscopy should be performed on the lesional target area, and should not overlap with the site of skin microbiome collection. Trichoscopy could overlap with the site of tape stripping or biopsy if needed, but should be performed first. The number of hairs, hair diameter, and hair density will be measured via fotofinder trichovision.

8.1.8 Hair Line Measurements

Hair line measurements will be performed at the visits specified in Table 1. Lateral canthus (right and left) to hairline, lower glabellar crease to hair line, top of frontalis muscle to hair line, and mid brow to hair line (right and left) will be measured using a disposable paper ruler.

8.2 Safety Assessments

8.2.1 Vital Signs

The following vital signs will be recorded at the visits specified in Table 1 (Cohort 1) and Table 2 (Cohort 2) with the subject in a seated position, after having sat calmly for at least 5 minutes: systolic and diastolic blood pressure (mmHg), pulse (bpm), and body temperature (°C).

Weight (kg) and height (cm) will be collected at the screening visit. Weight (kg) will also be collected at other visits specified in Table 1 (Cohort 1) and Table 2 (Cohort 2).

If deemed appropriate by the investigator, clinically significant findings in the vital signs will exclude a subject from trial participation. For Cohort 1 only, any abnormal finding related to vital signs that the investigator considers to be clinically significant must be recorded as an AE.

8.2.2 Complete Physical Examination

For subjects in Cohort 1 only, the following sites/systems will at least be included in the complete physical examination, which will be performed at the visits specified in Table 1:

- General appearance
- Dermatological (except FFA)
- Head, eyes, ears, nose, throat (HEENT)
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

Information for all physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a subject from trial participation. Any significant change will be reported as an AE in the source document and eCRF.

8.2.3 Brief Physical Examination

The following sites/systems will at least be included in the brief physical examination that will be performed at the visits specified in Table 1 (Cohort 1) and Table 2 (Cohort 2):

- General appearance

- Dermatological (except FFA)
- Respiratory
- Cardiovascular
- Abdominal

If deemed appropriate by the investigator based on the subject's condition, a complete physical examination as described in Section 8.2.2 can be performed instead of a brief examination.

Information for all physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a subject from trial participation. For Cohort 1 only, any significant change will be reported as an AE in the source document and eCRF.

8.2.4 Clinical Laboratory Tests

For subject in Cohort 1 only, laboratory tests will be performed at the visits specified in Table 1. The tests will include hematology with differential, a standard chemistry panel (chemistry includes liver function tests), TSH with reflex free T4 (screening), serum pregnancy test (screening) or urine pregnancy test (at other visits) for women of childbearing potential (WOCBP). The specific tests in these panels are listed in Table 7.

Table 7: Clinical Laboratory Testing (Cohort 1)

Laboratory Testing	Tests Included
Hematology	HCT, Hgb, MCH, MCHC, MCV, MPV, PLT, RBC, WBC, and differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils relative and absolute)
Biochemistry	Albumin, alkaline phosphatase, ALT, AST, chloride, creatinine (enzymatic), GGT, glucose random, LDH, potassium, sodium, total bilirubin, triglycerides, urea (BUN), uric acid
Urine pregnancy test	For female subjects of childbearing potential (at each visit, except screening)
Laboratory tests required at screening only	β-hCG for female subjects of childbearing potential Serology (HBV (HBsAg, anti-HBc), HCV, HIV) TSH with reflex free T4 (ie, free T4 will be performed only if TSH value is abnormal)

Abbreviations: ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; AST, aspartate aminotransferase; β-hCG, β-human chorionic gonadotropin; BUN, blood urea nitrogen; GGT, gamma-glutamyl-transferase; HBsAg, hepatitis B surface antigens; HBV, hepatitis B virus; HCT, hematocrit; HCV, hepatitis C virus; Hgb, hemoglobin; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PLT, platelets; RBC, red blood cell (count); TSH, thyroid-stimulating hormone; WBC, white blood cell (count).

In case of a screening laboratory value abnormality, the test can be repeated once within the original screening time window, if the investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

If deemed appropriate by the investigator, clinically significant findings in clinical laboratory testing will exclude a subject from trial participation. Any clinically significant value will be reported as an AE.

8.2.5 Electrocardiogram

For subjects in Cohort 1, a twelve-lead ECG will be performed as a safety assessment at the visit specified in Table 1. Clinically significant findings in the ECG should exclude a subject from study participation (as deemed appropriate by the investigator). Any clinically significant value will be reported as an AE.

8.2.6 Local Tolerability Assessments

For subjects in Cohort 1, subject local tolerability assessments will be performed at the visits specified in Table 1. On Day 1 and Week 12, the assessment will be performed approximately 30 minutes after the IMP application at the site with a recall period of 30 minutes. At other visits, the subject's local tolerability assessment will be done before the IMP application with a recall period of 7 days (worst over the last 7 days). The subject will evaluate stinging/burning at the application site using the scale described in Table 8.

Table 8: Subject Assessment of Local Tolerability after IMP Application

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

Abbreviation: IMP, investigational medicinal product.

The subject's assessment of local tolerability may be reported as an AE at the discretion of the investigator, even if the investigator does not suspect a local skin reaction related to application of IMP (reporting of stinging/burning by the subject).

8.3 Pharmacodymanic Assessments

For subjects in Cohort 1, skin microbiome samples and skin biopsies will be collected in all subjects. Adhesive tape strip samples collection is optional and will be performed per investigator's judgement (based on available skin area on the scalp). However, every effort should be made to collect tape strip samples in all subjects.

For subjects in Cohort 1, it is preferred that the skin microbiome samples, tape strips (when applicable), and skin biopsies come from the same lesional target area. If needed, a second lesional

target area could be selected to allow for skin samples collection and the hair count/trichoscopy assessment. If two lesional target areas are selected, they should be of similar severity.

In addition, lesional skin biopsies should be as close as possible from the area of the skin tape stripping and preferably from the target area. Lesional skin tape strips could be collected from the same area where trichoscopy/hair counts is performed. Other assessments need to be done on different areas of the lesional target area(s) (ie, they should not overlap).

8.3.1 Skin Biopsies

The skin will be cleaned, disinfected, and anesthetized before skin biopsies are performed. Sterile gauze will be used to absorb any bleeding. The biopsy sites will be sutured if necessary.

Details about the collection, processing, handling, storage and shipping of biopsy samples will be provided in the laboratory manual.

Cohort 1:

On Day 1, all subjects will have 2 skin biopsies (4-mm) collected prior to the first IMP application (1 from a lesional hair follicle within the target area and 1 from a non lesional hair follicle [eg, on the occipital scalp]). On Week 12, 1 skin biopsy (4-mm) will be collected from a hair follicle within the lesional target area (outside the scar of previous biopsies). Each biopsy will be split in half. One part will be used for IHC and the other part will be used for gene expression analysis.

Cohort 2:

On Day 1, all healthy subjects will have 2 skin biopsies (4-mm) that include hair follicles collected on healthy skin at similar matched areas of subjects with FFA (ie, 1 from frontal scalp area and 1 from occipital scalp area). Each biopsy will be split in half. One part will be used for IHC and the other part will be used for gene expression analysis.

8.3.2 Tape Stripping

Tape stripping is a non-invasive procedure where superficial skin cells is collected using tape strips. For each sampled site, approximately 20 tape strips units will be placed and removed from the exact same site one after the other.

Details about the collection, handling, storage and shipping of tape stripping samples will be provided in the laboratory manual.

Cohort 1:

Adhesive tape strip collection is optional for subjects in Cohort 1 and will be collected per investigator's judgement (based on available skin area on the scalp). However, every effort should be made to collect tape strip samples in all subjects.

On Day 1, skin tape strips will be collected prior to the first IMP application from lesional skin and from nonlesional skin (eg, on the occipital scalp). On Week 12, skin tape strips will be collected at the same location of the lesional skin.

Lesional tape strip samples should ideally be collected in the lesional target area. However, if the lesional target area is not large enough to accommodate the tape stripping, tape strips can be collected adjacent/close to the target area. The tape strip area can be a combination of lesional and non lesional skin (or peri-lesional skin) on the scalp, as long as this area will be treated with the IMP. If possible, tape stripping should be performed on non-hair bearing skin.

Cohort 2:

On Day 1, skin tape strips will be collected on non-hair bearing healthy skin at a similar matched area of subjects with FFA (ie, on the forehead, as close as possible to the frontal scalp area).

8.3.3 Skin Swabs for Microbiomes Analysis

Collection of skin microbiome samples is a non-invasive procedure where a swab is passed along the skin. Skin swabs for microbiome analysis must be collected prior to the tape stripping and skin biopsies.

Details about the collection, handling, storage and shipping of microbiome samples will be provided in the laboratory manual.

Cohort 1:

On Day 1, skin swab for microbiome analysis will be collected for all subjects prior to the first IMP application (1 from the target area [lesional skin] and 1 from an uninvolved occipital scalp area). On Week 12, skin microbiome will be collected at the same location of the lesional skin of the target area.

Cohort 2:

Two skin swab samples for microbiome analysis will be collected on healthy skin at similar matched areas of subjects with FFA (ie, 1 on frontal scalp area and 1 from occipital scalp area).

8.4 Other Assessments

8.4.1 Target Area Identification

For subjects in Cohort 1 only, a lesional target area on the scalp (eg, frontal, periauricular, or temporal area) and a non lesional area on the scalp (eg, occipital scalp) will be identified. The lesional target area will be within the lesional treated area of FFA and should be the most active area with regards to erythema and scaling as per investigator's judgment. To be eligible for this trial, subjects must have a lesional target area with a perifollicular erythema score ≥ 2 and a perifollicular scale score ≥ 2 on Day 1.

To allow for the hair count/trichoscopy assessment and all samples collection (ie, skin biopsies, tape stripping, and skin swabs), the lesional target area should be approximately 3 cm x 6 cm (or equivalent). However, as tape strips can be collected from the same area where trichoscopy/hair counts is performed or can be collected adjacent/close to the lesional target area (refer to Section 8.3.2 for details), a smaller lesional target area may be acceptable. If needed, two small target areas (totalling approximately the same size) could also be selected to allow for skin samples collection and hair count/trichoscopy assessment. If two lesional target areas are selected, they should be of similar severity.

In order to mark the lesional target area on the scalp, two 1-2 mm permanent tattoos will be made on the scalp by using a disposable 30-gauge needle to inject non-toxic ink in the epidermis of the skin.

A note on the location of the lesional target area should be made in the source document.

8.4.2 Medical Photography

For subjects in Cohort 1 only, medical photographs of the lesional target area and the entire scalp (including the frontal hair line and right and left hair line areas) will be performed at the visits specified in Table 1. Photographs should be taken prior to IMP application and skin sample collections (ie, skin biopsies, tape stripping, and skin microbiome). Photographs will be taken with the fotofinder device. Care will be taken to use the same magnification, and the same settings for each photograph at each visit in order to obtain comparable pictures.

Photographs will be identified as follows: trial number, subject number, visit name, and date. Photographs will be kept as electronic files on site and will be transmitted to the sponsor for review.

8.5 Adverse Events and Serious Adverse Events (Cohort 1 Only)

8.5.1 Definition of Adverse Event

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

8.5.2 Definition of Treatment-Emergent Adverse Event

A TEAE is any condition that was not present prior to treatment with the IMP but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

8.5.3 Definition of Serious Adverse Event

A SAE is any untoward medical occurrence that, at any dose has any of the following consequences:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important condition. Events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 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 hospitalization, development of drug dependency, or drug abuse.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

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

8.5.4 Classification of an Adverse Event

8.5.4.1 Relationship to Trial Treatment

The investigator will establish causality of the AE to the experimental treatment. The investigator should take into account the subject's history, most recent physical examination findings, and concomitant medications.

The following definitions will be used to determine causality of an AE:

- Not related: Temporal relationship of the onset of the AE, relative to the experimental treatment, is not reasonable, or another cause can explain the occurrence of the AE. Does not reappear or worsen upon re-challenge.
- 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.

8.5.4.2 Adverse Event Severity

The intensity of an AE is an estimate of the relative severity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: The symptom is barely noticeable to the subject and does not influence performance of daily activities. Treatment is not ordinarily indicated.
- Moderate: The symptom is sufficiently severe to make the subject uncomfortable, and performance of daily activities is influenced. Treatment may be necessary.
- Severe: The symptom causes severe discomfort, and daily activities are significantly impaired or prevented. Treatment may be necessary.

If the AE worsens in severity, the new severity, including date of severity change, should be recorded.

8.5.4.3 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 an 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.

8.5.4.4 Expectedness

Global Safety at LEO Pharma will assess the expectedness of each SAE in relation to the IMP. The relevant reference safety information document for this clinical trial is the delgocitinib cream Investigator's Brochure, Ed. 4, section 7.3.

8.5.5 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of trial personnel during trial visits and interviews of a trial subject presenting for medical care, or upon review by a trial monitor.

At all visits, the subject will be asked a non-leading question by the investigator about AEs, eg,: 'How have you felt since I saw you last?'. It is important that the investigator also observes the subject for any changes not reported by the subject and records these changes.

All AEs, including cutaneous and systemic reactions, will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to IMP (assessed only by those with the training and authority to make a diagnosis, ie, the investigator), and date of resolution/stabilization of the event. All AEs occurring while on trial must be documented appropriately regardless of relationship.

Trial site personnel will note the occurrence and nature of each subject's medical condition(s) present prior to the informed consent signature in the appropriate section of the source document and eCRF. During the trial, site personnel will note any change in the condition(s) and the occurrence and nature of any AE.

Any medical condition that is present prior to informed consent signature will be considered as part of medical history and not reported as an AE. However, if the trial subject's condition deteriorates after the consent signature, it will be recorded as an AE.

Should a subject experience an AE/SAE at any time after the informed consent signature until the end of participation in the trial, the event will be recorded as an AE in the source document and eCRF. The investigator is responsible for appropriate medical care of subjects during the trial. All non-serious AEs will be followed until the last subject's visit, unless additional follow up is required per medical judgment. If an SAE is ongoing at the end of trial, the subject will be followed up until the event is resolved or stable. For SAEs which have stabilized and from which the subject cannot be expected to recover during the trial or the safety follow-up period, e.g. chronic or stabilized conditions, the final outcome at the investigator's discretion should be reported as 'recovering/resolving' or 'not recovered/not resolved'. In addition, a statement detailing why the subject cannot be expected to recover during the trial, e.g. that the SAE has stabilized or is chronic, should be added to the narrative description of the SAE on the SAE form. Follow-up frequency will be performed at the discretion of the investigator.

Whenever possible, clinically significant abnormal laboratory results are to be reported using the diagnostic that resulted in the clinically significant abnormal laboratory results and not the actual abnormal test.

In the event the subject experiences a skin reaction that an allergic contact dermatitis is suspected, the event should be documented as an AE and the medication given, if any, recorded. The subject may be re-challenged using the assigned trial medication (patch test in the back) to confirm or rule out contact dermatitis.

8.5.6 Adverse Event Reporting

Investigators are responsible for monitoring the safety of subjects who are participating in this trial and for alerting the sponsor to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The AE term (verbatim) 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 (eg, 'allergic contact dermatitis').

For cutaneous AEs, the location of the AE relative to the treatment area will be recorded:

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

• Distant (>2 cm from the border of lesion(s) treated with IMP).

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

Action taken with IMP*:* any action taken with IMP as a consequence of the AE must be recorded (dose not changed, drug withdrawn, not applicable, unknown). Withdrawal from trial due to this AE: it must be recorded whether the AE led to withdrawal from the trial. Other action taken: any other action taken as a result of the AE must be recorded (none, concomitant medication, concurrent procedure).

8.5.7 Serious Adverse Event Reporting

Global Safety at LEO Pharma will be the pharmacovigilance unit responsible for the overall pharmacovigilance process for this trial. All SAEs, related to the trial treatment or not, occurring during the course of the trial must be reported on an SAE form (paper) to Global Safety at LEO Pharma (see below contact information) immediately without undue delay within 24 hours of the knowledge of the occurrence (this refers to any AE that meets one or more of the aforementioned serious criteria). This report should contain amongst others an assessment of available information on seriousness, severity, causal relationship to the IMP or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event. For more details regarding reporting of any SAE, please see the guidance text on the SAE form. Additionally, Global Safety at LEO Pharma may request further information in order to fully assess the SAE. The investigator must forward such information to LEO Pharma upon request by fax or e-mail (see contacts details below). The Innovaderm project team should also be informed of any SAE at the same time as Global Safety at LEO Pharma using the below contact information.

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

The SAE reporting period ends at the end of the follow-up period. SAEs occurring after the completion of the clinical trial should not be routinely sought or recorded. However, such events should be reported to Global Safety at LEO Pharma and the Innovaderm project team (see contact details below) if the investigator becomes aware of them.

Reporting should be done by sending the completed SAE form to the following e-mail addresses (faxing can also be done as a second option in case e-mailing is not possible).

Safety Contact Information: Global Safety at LEO Pharma
E-mail: drug.safety@leo-pharma.com
Fax: +45 7226 3287

AND

Innovaderm project team:
E-mail: EXP2228_SAE@innovaderm.com

Global Safety at LEO Pharma will inform the LEO medical monitor within 1 business day of awareness of a new SAE. Global Safety at LEO Pharma will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Global Safety at LEO Pharma will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

Global Safety at LEO Pharma will manage the expedited reporting of relevant safety information to concerned regulatory agencies in accordance with local laws and regulations.

Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis using documents such as Investigator Periodic Safety Update and/or any revised version of the IB.

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

8.5.8 Pregnancy Reporting

If a female subject becomes pregnant during the trial and up to 4 weeks after the end of the trial, the subject should inform the site as soon as possible. Upon confirmation of the pregnancy, the female subject will be discontinued from the trial. The investigator must complete a trial-specific pregnancy form upon confirmation of a pregnancy and send it to Global Safety at LEO Pharma within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE reporting) using the (paper) pregnancy form (part I). Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The investigator will follow the pregnancy until completion or until pregnancy termination and, in the case of a live-born offspring, to 1 month of age in that infant. The investigator should notify Global Safety at LEO Pharma and Innovaderm using the (paper) pregnancy form (part II) within 24 hours of first knowledge of the outcome as a follow-up to the

initial pregnancy form. All pregnancies should be reported to the sponsor and, when applicable, to the ethics committee.

8.5.9 Adverse events of special interest (AESI)

An AESI is an event type of scientific and medical concern specific for the product or development program, for which additional monitoring may be appropriate. Such an event might warrant further investigation in order to further characterize it.

Deep vein thrombosis/Pulmonary embolism is considered AESI in this trial and will require additional details to be recorded. LEO Pharma may request that the investigator forward additional test results, as appropriate. An AESI may be serious or non-serious. Serious AESIs require expedited reported via the SAE form as described in Section 8.5.7 in addition to the requirements specified below.

The additional information that will be collected is:

- Risk factors such as:
  - Previous thromboembolism (record as medical history)
  - Family history of deep vein thrombosis/pulmonary embolism or other cardiovascular/blood-clotting disorders
  - Genetic disorders that might increase the risk for thrombosis (record as medical history)
  - History of cancer (record as medical history)
  - Recent venous catheter placement (record as medical history)
  - Current smoker (record as tobacco smoking history)
  - Hormonal contraception/hormonal replacement therapy (record as concomitant medication)
  - Trauma or surgery (record as per protocol)
  - Immobilisation (e.g. prolonged bed rest or sitting for long periods)
  - None
- Method of verification may include:
  - Clinical evaluation
  - Image-verified
  - Laboratory test(s)

8.5.10 Medication error

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

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

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

Inappropriate schedule of product administration where a clinical consequence occurred or could have occurred should be recorded based on investigator judgement.

Treatment non-compliance (including missed doses) where no clinical consequence occurred or could have occurred should not be recorded as medication errors. See Section 6.3.2 for recording of treatment compliance.

Medication error must be recorded on the AE form in the eCRF. In addition, any clinical consequences of the medication error must be recorded as separate AEs on the AE form. If the AE originating from the medication error qualifies as an SAE, expedited reporting is required (Section 8.5.7).

8.5.11 Misuse or Abuse

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

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

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

Misuse and abuse must be recorded on the AE form in the eCRF. In addition, any clinical consequences of misuse or abuse must be recorded as separate AEs on the AE form. If the AE originating from the misuse or abuse qualifies as an SAE, expedited reporting is required (Section 8.5.7).

8.5.12 Aggravation of condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s) compared to screening must be reported as an (S)AE in accordance with Section 8.5.5.

Worsening of FFA is captured by efficacy assessments and will not be recorded as an AE.

8.6 Procedural Complications (Cohort 2 Only)

For subjects in Cohort 2, procedural complications will be reported instead of AEs.

For the purpose of this trial, a procedural complication is defined as any untoward medical event experienced by a subject that has signed an ICF for the trial, such as infection, bleeding, and/or pain, that the investigator believes to be causally related to the trial procedures performed at Day 1 visit or at the optional visit. Subjects will receive appropriate treatment as needed for any procedural complications that arise.

For the purpose of this trial, a serious procedural complication is any untoward medical event related to the trial procedures that has any of the following consequences:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Any medical condition that is present prior to the first sample collection on Day 1 will be considered as part of medical history and not reported as a procedural complication. Should a subject experience an event that he believes to be causally related to the trial procedure performed on Day 1 or at the optional follow-up visit (after sample collection), the event will be recorded as a procedural complication. Any procedural complications whether observed by site personnel or reported spontaneously by the subject will be described in the source document and eCRF.

Any serious procedural complication (this refers to any procedural complication that meets one or more of the aforementioned serious criteria) occurring during the trial must be reported on a serious procedural complication form as per the instructions in Section 8.5.7.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

From Del Duca et al. (2020) paper[1], the difference in log2-fold changes (SD*) between FFA patients and healthy controls are reported to 4.851 (4.411), 5.298 (5.512) and 4.559 (4.891) for CXCL9, CXCL10 and IFN-γ, respectively.

A sample 30 subjects are randomized in an equal manner (1:1) to delgocitinib cream 20 mg/g or vehicle cream. It is expected that a reduction of at least 90% from baseline to Week 12 for the delgocitinib cream 20 mg/g treated subjects compared to only 5% in the vehicle group, normalized to healthy controls, will be observed.

With the above assumptions, the trial should have at least 80% disjunctive power, i.e. a statistically significant difference (tested at 5% one-sided level in an independent two-sample t-test) can be shown with at least 80% probability, in at least one of the genes, assuming no correlation between the tests and same level of variation as reported in the Del Duca et al. (2020) paper[1].

*Derived from the reported p-values coming from a t-test comparing lesional FFA biopsy data (N=12) to data from healthy controls (N=8).

9.2 Populations for Analyses

Cohort 1:

Efficacy will be evaluated on the basis of the full analysis set (FAS). A supportive analysis will also be conducted on the per-protocol (PP) analysis set.

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

PD analysis set: This analysis set is a subset of the FAS and will include all subjects who have at least one assessment of PD parameters.

Per-protocol (PP) analysis set: This analysis set will include all subjects who were randomized, who received at least one dose of IMP and who at least one post dose efficacy measurement with no major protocol deviations affecting the efficacy evaluations. All subjects will be analyzed according to the treatment group that they actually received during the vehicle-controlled period.

Safety analysis set (vehicle-controlled treatment period): This analysis set will include all subjects who received at least one dose of the IMP. All subjects will be analyzed according to the treatment group that they actually received during the vehicle-controlled period.

Safety analysis set (OLE): This analysis set will include all subjects who entered the OLE and received at least one dose of delgocitinib 20 mg/g during the OLE.

Cohort 2:

Safety analysis set: This analysis set will include all subjects who had at least one skin sample collected.

9.3Statistical Analyses

9.3.1 General Approach

Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation (SD), median, minimum, maximum, first (Q1) and third (Q3) quartiles. Categorical variables will be presented in tables as frequencies and percentages.

All details regarding the efficacy and safety variable definitions, analyses strategy, statistical justification, and techniques for handling missing values will be detailed in a separate statistical analysis plan (SAP) that will be prepared before the database is locked and any analyses are undertaken. Any deviation(s) from the SAP will be described and justified in the final report, as appropriate. Statistical analysis related to molecular signature changes/PD analyses (ie, skin biopsies, tape strips, and skin microbiome) will be described in a separate SAP prepared by the specialty laboratory in charge of these analyses.

All statistical tests will be two-sided and will be performed with a significant level of 0.05, unless otherwise specified in the SAP.

9.3.2 Baseline

Baseline will be defined separately for the vehicle-controlled treatment period and OLE as follows:

- Vehicle-controlled treatment period:

  For both the safety and exploratory efficacy analyses, the baseline will be defined as the last non-missing assessment prior to the first trial treatment dose (including unscheduled assessments). If the last non-missing assessment is performed on the same date as the first trial treatment and time is not available, the assessment will be considered as baseline, except for AEs and medications starting on the first trial treatment dose date which will be considered post-baseline.

- Open-label extension period:

  For the safety analyses, the OLE baseline will be defined as the last non-missing assessment prior to the first delgocitinib cream 20 mg/g dose. This definition will be used for summarizing the change from the OLE baseline for the subject who entered OLE period.

  For the exploratory efficacy analyses, the baseline will be defined as the last non-missing assessment prior to the first trial treatment dose (including unscheduled assessments) from the vehicle-controlled treatment period for all subjects.

Change from baseline is defined for both the vehicle-controlled treatment period and OLE as the post-baseline value minus the baseline value unless otherwise specified. Percent change from baseline will be calculated as follows: Percent change from baseline = (Change from baseline / Baseline) x 100

For the pruritus NRS, burning sensation NRS, and pain NRS, the baseline scores will be defined as the average of all non-missing daily 24-hour NRS scores reported over the last 7 days prior to randomization (prior to the first application of the IMP).

9.3.3 Efficacy Analyses

9.3.3.1 Vehicle-Controlled Treatment Period

The comparison between the groups for the exploratory efficacy endpoints will be done using a mixed model repeated measures (MMRM), where the change from baseline will be the dependent variable; the treatment group, the visit, and an interaction term for the treatment-by-visit will be the fixed effects; and the baseline value will be the covariate.

The exploratory efficacy endpoints involving change from baseline will be analyzed at each time point using the same approach (i.e., MMRM) as described for the primary efficacy analysis.

The other efficacy endpoints involving proportions of pruritus NRS, burning sensation NRS, and pain NRS will be analyzed using a Chi-squared test at each visit.

The primary efficacy analysis will be done using the FAS, and the PP analysis set will be used as supportive analysis. No imputation will be performed for the continuous endpoints subjected to an MMRM.

For the analyses of binary data, imputation of the last observation carried forward (LOCF) for any missing value will be performed.

9.3.3.2 Open-Label Extension Period

These efficacy outcomes will be measured at scheduled visits after Week 12. The following endpoints will be assessed in the OLE:

- Continuous variables: observed value and change (percent) from baseline in LPPAI, FFASS, target area perifollicular scale score, target area perifollicular erythema score, pruritus NRS, burning sensation NRS, pain NRS, and target area hair counts/trichoscopy via fotofinder trichovision.

The above endpoints will be summarized by visit using descriptive statistics with following considerations:

- Summaries will be provided for 1) treatment group in OLE and for 2) randomized treatment groups in the vehicle-controlled treatment period.
- Change from baseline in continuous variables will be analyzed using change from vehicle-controlled treatment period baseline.

9.3.4 Safety Analyses

9.3.4.1 Vehicle-Controlled Treatment Period

Cohort 1:

All safety data, including AEs and SAEs will be presented and tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) classification. Descriptions of AEs will include the start date, the stop date (if it resolved), the severity and seriousness of the AE, the causality of the AE to IMP, and the outcome. The focus in this protocol will be the number of treatment-emergent adverse events (TEAEs).

Adverse events will be considered in vehicle-controlled treatment period or OLE depending on the onset date – if the AE onset date was before Week 12, the AE will be considered as a vehicle-controlled treatment period AE. If the AE had an onset on or after Week 12, the AE will be considered as an OLE AE.

Reported AEs will be summarized by the number of subjects reporting the events, as well as by System Organ Class (SOC), PT, severity, seriousness, and relationship to IMP. For the summary of AEs by severity, each subject will be counted only once within a SOC or a PT by using the AEs with the highest intensity within each category for each analysis. For the summary of AEs by relationship to IMP, each subject will be counted only once within a SOC or a PT by using the AEs with the greatest reported relationship within each category. For the summary of AEs by relationship to IMP and severity, each subject will be counted only once within a SOC or a PT by using (1) the greatest reported relationship followed by (2) the highest reported intensity.

All information pertaining to AEs noted during the trial will be listed by subject, detailing verbatim, SOC, PT, start date, stop date, intensity, outcome, and relationship to IMP. The AE onset will also be shown relative (in number of days) to the day of IMP administration. Serious adverse events will be tabulated by treatment group, relationship to the IMP, and a reference to the occurrence of the SAEs to the relative day of dosing.

AESIs will be listed. No narratives for AESIs will be written in the study report.

Results from laboratory analyses and vital signs will be tabulated by treatment and visit using descriptive statistics. The value at each visit as well as the change from baseline will be presented descriptively.

Clinically significant changes in laboratory analyses and vital signs, and new findings on local tolerability assessments and physical examination will be recorded as AEs.

Concomitant medications will be coded with the world health organization (WHO)-Drug Dictionary and listed by subject. Summary of medication classes will also be tabulated.

No inferential statistics will be done on safety variables.

Cohort 2:

Procedural complications will be presented and tabulated according to MedDRA classification. Descriptions of procedural complications will include the start date, the stop date (if it resolved), the severity and seriousness of the procedural complication, and the outcome.

Reported procedural complications will be summarized by the number of subjects reporting the events, as well as by SOC, PT, severity, and seriousness. For the summary of procedural complications by severity, each subject will be counted only once within a SOC or a PT by using the procedural complications with the highest intensity within each category for each analysis.

All information pertaining to procedural complications noted during the trial will be listed by subject, detailing verbatim, SOC, PT, start date, stop date, intensity, and outcome. The procedural complication onset will also be shown relative (in number of days) to the Day 1 skin sample collection.

9.3.4.2 Open-Label Extension Period

Safety analyses will follow general considerations in previous Section 9.3.4.1 with the following exceptions:

- Summaries will be provided for 1) treatment group in the OLE and for 2) randomized treatment groups in vehicle-controlled treatment period.
- Change from baseline will be analyzed using change from vehicle-controlled treatment period baseline for subjects who received delgocitinib during the vehicle-controlled treatment period, and change from OLE baseline for subjects who received placebo during the vehicle-controlled treatment period.

Only descriptive statistics will be presented.

9.3.5 Molecular Signature Changes Analyses

Molecular signature changes analyses will be evaluated on the basis of the PD analysis set. A MMRM will be used to detect any overall differences in the treatment effect at Week 12 compared to baseline in the molecular measurements. This formulation intrinsically models the within patient correlation structure as in the case of a paired t-test. This approach introduces less bias than restricting the analysis for those patients who completed the trial. Time points (baseline, Week 12), treatment group (active, vehicle, and healthy), and tissue (lesional and non-lesional) will be considered as fixed factors, while participant ID will be included as random factor.

9.3.6 Other Analyses

Descriptive summaries of baseline characteristics, including demographic data, prior and concomitant therapy, and subject disposition will be presented. In addition, a list of subjects who discontinued from the trial will be provided.

Protocol deviations will be summarized by treatment and category.

9.3.7 Planned Interim Analyses

No interim analysis is planned in this trial.

10 REGULATORY, ETHICAL, AND TRIAL OVERSIGHT CONSIDERATIONS

10.1 Local Regulations/Declaration of Helsinki

This trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH Tripartite Guideline for GCP and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

10.2 Ethical Review

It is the understanding of the sponsor that this protocol (and any amendments) as well as appropriate consent procedures, will be reviewed and approved by a REB/IRB. This board must operate in accordance with the current federal regulations. If the site has a local ethics committee, a letter or certification of approval will be sent by the investigator to the sponsor (or CRO) before initiation of the trial and also whenever subsequent modifications to the protocol are made.

10.3 Informed Consent Process

An ICF describing in detail the trial treatment (for Cohort 1 only), trial procedures, and risks will be given to the subject, along with an assent form when required.

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulation), to obtain written informed consent from each individual participating in this trial, after adequate explanation of the aims, methods, objectives, and potential hazards of the trial.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the trial and continues throughout the individual's trial participation. Consent forms will be IRB/REB approved, and the subject will be asked to read and review the document. The investigator will explain the research trial to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the trial and of his or her rights as a research subject. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the trial with their family or surrogates or think about it prior to agreeing to participate.

The subject will sign the informed consent document prior to any procedures being done specifically for the trial. Subjects must be informed that participation is voluntary and that they may withdraw from the trial at any time for any reason, without prejudice. A copy of the signed informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any trial-specific procedures.

The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this trial.

If new safety information results in significant changes in the risk/benefit assessment, or if any new information becomes available that may affect the willingness of a subject to continue to participate, the consent form should, if necessary, be reviewed and updated by the IRB/REB. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form, and asked to give their consent to continue in the trial.

10.4 Trial Discontinuation and Closure

This trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for trial suspension or termination, will be provided by the suspending or terminating party to trial subjects, investigators, the sponsor, and regulatory authorities. If the trial is prematurely terminated or suspended, the principal investigators will promptly inform trial subjects and the IRB/REB, and will provide the reason(s) for the termination or suspension. Trial subjects will be contacted, as applicable, and be informed of changes to trial visit schedule.

Circumstances that may warrant termination or suspension of the trial include, but are not limited to the following:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete or evaluable
- Scientific or corporate reasons

The trial may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB/REB, and/or FDA.

10.5 Confidentiality and Privacy

Subject confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the trial protocol, documentation, data, and all other information generated will be held in strict confidence.

The investigator must assure that the subjects' anonymity will be maintained and that subjects' identities are protected from unauthorized parties. On CRF or other documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject log relating codes with the names of subjects. The investigator should maintain in strict confidence documents not for submission to LEO Pharmaceutical A/S (e.g., subjects' written consent forms).

All research activities will be conducted in a setting as private as possible.

The study monitor, other authorized representatives of the sponsor, and representatives of the IRB, regulatory agencies, or pharmaceutical company supplying IMP may inspect all documents and

records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this trial. The clinical site will permit access to such records.

The trial subject's contact information will be securely stored at each clinical site for internal use during the trial. At the end of the trial, all records will continue to be kept in a secure location for as long a period as dictated by the applicable legal or regulatory requirements, the reviewing IRB, institutional policies, or sponsor requirements.

10.6 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial subjects are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP guidelines, and with applicable regulatory requirement(s). Details of clinical site monitoring will be documented in a Monitoring Plan. Centralized monitoring, which consist of remote review of accumulating data from all sites, will be performed as detailed in the Centralized Monitoring Plan.

10.7 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of trial conduct, data and biological specimen collection, documentation, and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks, which will be run on the database, will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

During the trial, the sponsor or its representative will conduct monitoring visits at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries on the eCRFs, IMP accountability, compliance with regulatory requirements, and continued adequacy of the site and its facilities.

The site may be audited, monitored, or inspected by a quality assurance officer named by the sponsor, by the REB or IRB, and/or by the regulatory authorities. The investigator will be given notice before an audit occurs and will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested. The site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

10.8 Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

The investigator must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. These documents should be

classified into two separate categories: investigator's study files and subject clinical source documents.

The investigator must maintain source documents for each subject in the trial. These source documents will consist of case and visit notes (clinical medical records) containing demographic and medical information and the results of any tests or assessments. All information on the eCRFs must be traceable to the source documents in the subject's file. Data not requiring a written or electronic record will be defined before trial start and will be recorded directly on the eCRFs, which will be documented as being the source data.

The records should be retained by the investigator according to ICH guidelines, local regulations, or as specified in the Clinical Trial Agreement, whichever retention period is longer.

Subject data will be entered by site personnel using Medrio, a web-based EDC and reporting system. This application will be set up for remote entry. Medrio Inc. is the developer and owner of Medrio. The EDC software has been fully validated and conforms to Title 21 of the Code of Federal Regulations, Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been fully trained. Designated investigator staff will enter the data required by the protocol into the eCRFs using this web-based application. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before confirming the data. The investigator must certify that the data are complete and accurate by applying an electronic signature to the eCRFs.

The data collected will be encoded and stored electronically in a database system. Validated data may subsequently be transferred to the sponsor.

10.9 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The non-compliance may be either on the part of the subject, the investigator, or the trial site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. The clinical research associate (CRA) must ensure that a prompt action is taken to secure compliance. If a non-compliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the CRO and the Sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

Protocol deviations must be sent to the reviewing IRB per their policies. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.10 Publication Policy

The publication policy will be addressed in the Research and Financial Agreement with the site, and all details outlined in the agreement will apply to this protocol. The trial will be registered on ClinicalTrials.Gov prior to the first subject being dosed.

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APPENDIX A: Lichen Planopilaris Activity Index (LPPAI) [7]

Date of visit				
LPPAI (see below)				
SCALE: 0-3 A Pruritus				
B Pain				
C Burning				
D Erythema				
E Perifollic erythema				
F Perifollicular scale				
Crusting				
Pustules				
Pull test: Anagen/Total **(0=-, 1=+)**				
Spreading? **no (0) ? (1) yes (2)**				

LPPAI (0-10) = (A+B+C+D+E+F)/3 + 2.5(pull test) + 1.5(spread/2)

Scale: **0** = negative **1**= +/- **2** = + **3** = ++,+++

APPENDIX B: Frontal Fibrosing Alopecia Severity Score [8]

CLINICAL SIGNS			
1. HAIRLINE RECESSION (measurement of band-like scarring area)			**PUNCTUATION**
Frontal **(x2)**	<1cm (1) 1-2.99cm (2) 3-4.99cm (3) 5-6.99cm (4) >7cm (5)		__ / 10
Temporal left			__ / 5
Temporal right			__ / 5
2. LOSS OF EYEBROWS			
No (0) / Partial (0.5) / Total (1)			__ / 1
EXTENT OF ALOPECIA SCORE			**__ / 21**
3. PERIFOLLICULAR INFLAMMATION			
A) SEVERITY			
Erythema	No / Mild / Severe	0 / 0.1 / 0.2	__ / 0.2
Hyperkeratosis		0 / 0.5 / 1	__ / 1
B) EXTENT (along the frontotemporal hairline)			
Erythema	<25% / 25-75% / >75%	0 / 0.1 / 0.2	__ / 0.2
Hyperkeratosis		0 / 0.5 / 1	__ / 1
ASSOCIATED SYMPTOMS			
1. PRURITUS			
Severity	No (0) Mild / Occasional (0.1) Severe / Daily (0.2)		__ / 0.2
			__ / 0.2
Frequency			
2. PAIN			
Severity	No (0) Mild / Occasional (0.3) Severe / Daily (0.6)		__ / 0.6
Frequency			__ / 0.6
GRADE OF INFLAMMATION SCORE			**__ / 4**
TOTAL FFASS SCORE			**__ / 25**

APPENDIX C: Numerical Rating Scale

Pruritus NRS

On scale from 0 ("no itch") to 10 ("worst imaginable itch"), how was your worst itch due to your frontal fibrosing alopecia in the past 24 hours? Please select one number.

Numeric Rating Scale										
0	1	2	3	4	5	6	7	8	9	10
No itch										Worst imaginable itch

Modified from: http://www.pruritussymposium.de/numericalratingscale.html

Burning Sensation NRS

On scale from 0 ("no burning sensation") to 10 ("worst imaginable burning sensation"), how was your worst burning sensation due to your frontal fibrosing alopecia in the past 24 hours? Please select one number.

Numeric Rating Scale										
0	1	2	3	4	5	6	7	8	9	10
No burning sensation										Worst imaginable burning sensation

Pain NRS

On scale from 0 ("no pain") to 10 ("worst imaginable pain"), how was your worst pain due to your frontal fibrosing alopecia in the past 24 hours? Please select one number.

Numeric Rating Scale										
0	1	2	3	4	5	6	7	8	9	10
No pain										Worst imaginable pain

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