NOVARTIS

Novartis Research and Development

AIN457

Clinical Trial Protocol CAIN457S12201 / NCT04300296

A proof of concept study to evaluate the efficacy, safety and tolerability of secukinumab 300 mg over 32 weeks in adult patients with biopsy-proven forms of lichen planus not adequately controlled with topical therapies - PRELUDE

Document type:	Clinical Trial Protocol Amendment
EUDRACT number:	2019-003588-24
Version number:	02 (Clean)
Clinical Trial Phase:	II
Release date:	26-Oct-2020

Property of Novartis
Confidential
May not be used, divulged, published, or otherwise disclosed
without the consent of Novartis
Clinical Trial Protocol Template Version 2.0 dated 01-Aug-2018

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BDR	Bioanalytical Data Report
BSA	Body Surface Area
BSL	Baseline
CFR	Code of Federal Regulation
ClinRO	Clinician reported outcome
CLP	Cutaneous lichen planus
[redacted]	[redacted]
CMO & PS	Chief Medical Office and Patient Safety
CO	Country organization
CRA	Clinical Research Associate
CRF	Case report form
CRO	Contract Research Organization
CSR	Clinical study report
CTRD	Clinical Trial Results Database
CTT	Clinical Trial Team
[redacted]	[redacted]
CVID	Common variable immunodeficiency
DDE	Direct data entry
DLQI	Dermatology Life Quality Index
[redacted]	[redacted]
EDC	Electronic Data Capture
[redacted]	[redacted]
EMA	European Medicines Agency
EOT	End of treatment
eSAE	electronic Serious Adverse Event
[redacted]	[redacted]
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFA	Frontal fibrosing alopecia
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-Glutamyl-Transferase
h	hour
H	Home administrations
HbA1c	Hemoglobin A1c

HBsAg	Hepatitis B surface antigen
HDL	High density lipoprotein
HIV	human immunodeficiency virus
HRQoL	Health-related quality of life
hs-CRP	High sensitivity C-reactive protein
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for use
[redacted]	[redacted]
IGA	Investigator's Global Assessment
IL-17A	Interleukin 17A
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLN	lower limit of normal
LLOQ	Lower limit of quantification
LP	Lichen planus
LPP	Lichen planopilaris
LPPAI	Lichen Planopilaris Activity Index
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MLP	Mucosal lichen planus
NCDS	Novartis Clinical Data Standards
NCT	National clinical trial
NRS	Numerical rating scale
OLP	Oral lichen planus
OLPSSM	Oral Lichen Planus Symptom Severity Measure
OTC	Over the counter
PBO	Placebo
PD	Pharmacodynamic(s)
PFS	Pre-filled syringe
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

PoC	Proof-of-concept
PPD	Purified protein derivative
PRO	Patient reported outcome
PSAD	Physician´s assessment of surface area of disease
PUVA	Psoralen and Ultraviolet A
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
QFT	QuantiFERON® TB-Gold test
QMS	Quality Management System
RAS	Randomized Analysis Set
RDC	Remote Data Capture
REU	Reticulations, erythema and ulcerations
RoW	Rest of the World
RPM	Revolutions Per Minutes
s.c.	subcutaneous
SAE	serious adverse event
SC	Steering Committee
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	Standard Operating Procedures
SST	Serum Separator Tubes
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TBL	total bilirubin
TNF	Tumor necrosis factor
ULN	upper limit of normal
ULQ	upper limit of quantification
US	United States of America
UVA	Ultraviolet A
UVB	Ultraviolet B
WHO	World Health Organization
Wk	Week
WoC	Withdrawal of Consent

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Estimand	A structured framework that translate the trial objective into a precise definition of the treatment effect that is to be estimated
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study that contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.

Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Amendment 02

Amendment rationale

The reason for this amendment is to allow the assessment of biopsies by local pathologists.

Other, minor points have been updated or corrected as well to further optimize the clinical trial protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined font for insertions.

Changes to the protocol include:

- Section 8.5.4 has been modified to allow the assessment of biopsies by local pathologists

Editorial revisions, clarifications and corrections have also been made throughout the protocol.

None of the changes are due to safety concerns and none of the changes have an impact on the conduct of the trial or alter in any way the treatment of study subjects.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

The changes herein do NOT affect the trial specific model ICF.

Summary of previous amendments

Amendment 01

Amendment rationale

There are three major reasons for this amendment:

The first one is an update of the IGA score specifications. Certain criteria of the score have been changed in a way that the score in its amended version is more specific regarding certain aspects of the disease, its clinical application has become easier and it now covers cases which were not covered before.

The second major reason is to allow the use of historical biopsies (if available) at screening for patients of all three subtypes of lichen planus instead of allowing it for the lichen planopilaris cohort only. This makes the trial more patient friendly and reduces the need for biopsies.

The third major reason is to adapt the protocol to pandemic/ epidemic related challenges and their potential longer lasting impact on the conduct of clinical trials. In case of a pandemic/ epidemic, sites are given the opportunity for home shipment of study drug and urine pregnancy tests, as well as phone calls for safety assessment. The purpose of this is to protect patients as well as site staff by reducing personal exposure and thereby reducing the risk for transmission of infectious diseases (e.g. COVID-19) while maintaining adequate safety monitoring.

Other, minor points have been updated or corrected as well to further optimize the clinical trial protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Changes to the protocol include:

- Table 2-1 has been modified to enlarge Patient assessment of itch to all LP sub-types
- Section 3, End of treatment and End of study have been further defined and flow of visits clarified, criteria for re-screening have been clarified
- Section 5.2, Inflammatory Bowel Disease has been added as an example to Exclusion criterion #15
- Section 6.1.3 has been corrected to enlarge the use of historical biopsy for inclusion to all LP subtypes
- Section 6.2.1, Section 6.2.2, List of allowed and forbidden medications has been corrected and clarified
- Section 6.7 and Section 6.7.2 have been modified to allow study drug shipment to subjects and home administration, as well as remote contact to collect safety information in case of pandemic / epidemic event

- Section 8 and Section 8.4 have been modified to allow study drug shipment to subjects and remote contact to collect safety information in case of pandemic / epidemic event
- Section 8, End of treatment and End of study have been further defined and flow of visits clarified, criteria for re-screening have been clarified,
- Section 8.1, criteria for re-screening have been clarified
- Table 8-1 has been modified to enlarge Patient assessment of itch to all LP sub-types and to enlarge the use of historical biopsy for inclusion to all LP subtypes, End of treatment and End of study have been further defined, and flow of visits clarified; timing of urine pregnancy tests has also been corrected
- Table 8-2, the Investigator's Global Assessment grading has been modified
- Section 8.3.2, Assessment scoring for Physician's assessment of surface area of disease has been corrected
- Section 8.4.2, Section 8.5.4 Timing of urine pregnancy tests has been corrected
- Section 8.5.4 has been corrected to enlarge the use of historical biopsy for inclusion to all LP subtypes
- Section 9.1.1, Section 9.1.2, Section 9.2, End of treatment and End of study have been further defined and flow of visits clarified
- Section 10.1.4, Need for requiring a signed pregnancy ICF to follow up on any pregnancy has been added

Editorial revisions, clarifications and corrections have also been made throughout the protocol.

Protocol summary

Protocol number	CAIN457S12201
Full Title	A proof-of-concept study to evaluate the efficacy, safety and tolerability of secukinumab 300 mg over 32 weeks in adult patients with biopsy-proven forms of lichen planus not adequately controlled with topical therapies - PRELUDE
Brief title	Study of efficacy and safety of secukinumab 300 mg in adult patients with biopsy-proven forms of lichen planus
Sponsor and Clinical Phase	Novartis/Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Lichen planus (LP) is an inflammatory disease affecting different locations of the body (skin, oral cavity, genitalia, scalp, and nails). Current therapies are mostly symptomatic. However, 30-50% of patients are refractory to available therapies and experience high burden of disease due to lack of clinical control, as well as significant psychological discomfort and social disability resulting in profoundly impaired quality of life. This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial assessing the efficacy and safety of secukinumab 300 mg in two different dosing regimens in patients with biopsy-proven forms of lichen planus, for which no systemic therapy is currently approved and which could be eligible for treatment with secukinumab.
Primary Objective(s)	The primary objective of this study is to evaluate the efficacy secukinumab when compared to placebo after 16 weeks of treatment, by comparing the proportion of patients achieving Investigator's Global Assessment (IGA) response where IGA response is defined as achievement of absolute IGA score less or equal 2 (IGA ≤2).
Secondary Objectives	Objective 1: to evaluate the efficacy of secukinumab 300 mg Q4W compared to placebo throughout 16 weeks in Treatment Period 1 and to evaluate the long term efficacy of secukinumab 300 mg Q4W throughout 32 weeks in Treatment Period 2 and evaluate the efficacy of secukinumab 300 mg Q2W in Treatment Period 2 by Investigator's Global Assessment (IGA), Dermatology Life Quality Index (DLQI), Physician Assessment of Surface Area of Disease (PSAD) for Skin Disease, Patient assessment of itch (Numerical Rating Scale - NRS), Reticular Erythematous Ulcerative (REU) score, Oral Lichen Planus Symptoms Severity Measure (OLPSSM) score, Patient assessment of pain (NRS), LPP Activity Index (LPPAI), SCALPDEX Questionnaire. Objective 2: to assess the safety and tolerability of secukinumab in subjects with lichen planus by adverse events (AEs), laboratory values, vital signs from baseline to end of study visit.
Study design	This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in approximately 108 patients with biopsy-proven lichen planus. The study consists of: Screening (up to 4 weeks), Treatment Period 1 (16 weeks), Treatment Period 2 (16 weeks). Subjects who prematurely

	discontinue the study, or who complete the study, will enter a post-treatment Follow-Up period (8 weeks).
Population	The study population will consist of adult subjects (≥ 18 years) with biopsy-proven lichen planus. It is planned to randomize approximately 108 subjects in approximately 36 study sites worldwide. At randomization, the subjects will be assigned to one of the 3 cohorts (predominant cutaneous lichen planus (CLP), predominant mucosal lichen planus (MLP) and lichen planopilaris (LPP)) according to the clinical features present.
Key Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. 2. Female and male patients ≥ 18 years of age. 3. Subjects must have biopsy-confirmed forms of cutaneous lichen planus (CLP), mucosal lichen planus (MLP), or active lichen planopilaris (LPP) eligible for systemic therapy based on the following criteria: · Rated IGA of ≥ 3 (moderate or severe) at screening and baseline **AND** · Inadequate response to topical corticosteroids of high - ultrahigh potency in the opinion of the investigator
Key Exclusion criteria	1. Clinical history suspicious for lichenoid drug eruption. 2. Lichen planus pigmentosus. 3. Clinical picture or history suspicious of paraneoplastic mucosal lichen planus. 4. Subjects whose lichen planus is a predominantly bullous variant. 5. Mucosal lichen planus of the oral cavity or gastrointestinal involvement requiring the patient to use parenteral nutrition or feeding tube. 6. Clinical picture of burnt-out cicatricial alopecia (alopecia of Brocque) 7. Patients diagnosed with frontal fibrosing alopecia (FFA) without active patches of LPP. 8. Previous exposure to any other biologic drug directly targeting IL-17A or IL-17RA (e.g. ixekizumab or brodalumab) or IL-23/p19 (e.g. tildrakizumab, guselkumab, risankizumab). 9. Hepatitis C antibody positive at screening unless viral load is 0.
Study treatment	1. Secukinumab 300 mg, provided as 2 s.c. injections of 1 ml prefilled syringe (PFS). Each 1 ml syringe contains 150 mg secukinumab. 2. Placebo, provided as 2 s.c. injections of 1 ml prefilled syringe (PFS).
Efficacy assessments	Efficacy assessments related to the primary and secondary objectives include: **Clinician Reported Outcomes (ClinRO)** assessed by the investigator • Investigator's Global Assessment (IGA) • Physician Assessment of Surface Area of Disease (PSAD) • Reticulation, Erythema and Ulcerations score (REU) • Lichen Planopilaris Activity Index (LPPAI) **Patient reported outcomes (PRO)** assessed by the subject: [redacted]

	• Patient assessment of itch (NRS) • Patient assessment of pain (NRS) • Oral Lichen Planus Symptom Severity Measure (OLPSSM) • Dermatology Life Quality Index (DLQI) [redacted] • SCALPDEX
[redacted]	[redacted]
Key safety assessments	• Evaluation of all Adverse Events (AEs) and Serious AEs (SAEs) • Physical examination • Vital signs • Laboratory evaluations (e.g. hematology, clinical chemistry) [redacted] • Pregnancy
Other assessments	[redacted]
Data analysis	In each cohort, for secukinumab 300 mg and placebo treatment groups, the proportion of subjects classified as IGA responders after 16 weeks of treatment, will be modeled with a binomial distribution. A neutral, non-informative Beta (1/3, 1/3) distribution will be used as the prior for the response rate for secukinumab and placebo treatment groups. Based on the priors and the observed primary outcome, posterior distributions for the response rate in secukinumab and placebo treatment groups will be computed respectively for each cohort. The posterior distribution of the difference of response rates over placebo will be obtained by simulations. The posterior probabilities for a positive treatment difference will be assessed according to the dual efficacy criteria as a guide to decision making. In each cohort, secukinumab treatment will be assessed separately in comparison to the placebo group. Subjects who do not complete the 16-week treatment will be considered as non-responders.
Key words	Lichen planus, LP, CLP, MLP, LPP, IL-17A, monoclonal antibody, AIN457, secukinumab, itch, pain, efficacy, safety

1 Introduction

1.1 Background

Lichen planus (LP) is a mucocutaneous, inflammatory disease of unknown etiology. First described in 1869 and deriving its name from the Greek word lειχήη, for 'tree moss', and the Latin word *planus*, for 'planar', lichen planus is a relatively uncommon and heterogeneous disorder that typically develops in middle-aged adults affecting the skin, the mucosae, or both (Tziotzios et al 2018). It is recurrent, and can present in different clinical subtypes based on the morphology of the lesions and the site of involvement.

Skin lesions of lichen planus (cutaneous lichen planus, CLP) are characterized by a subacute or chronically progressive appearance of polygonal purple papules often associated with severe itch. Mucosal lesions (mucosal lichen planus, MLP) present with usually bilateral white striations or plaques, either symptomatic or extremely painful due to their erosive nature, and localized in different areas (buccal mucosa, tongue and gingivae, genitalia, conjunctiva or esophagus). Lichen planopilaris (LPP) is considered a follicular variant of CLP and develops with active patches that, if untreated, lead to irreversible scarring and alopecia. LPP has a sexual predilection for females and can also be induced by hair transplantation or cosmetic facial surgery due to peri-operative immune-inflammatory responses (Gorouhi et al 2014).

Lichen planus (LP) estimated prevalence is in the range of 0.1 to 4 percent of the general population (Zakrzewska et al 2005). Oral or genital involvement occurs in 60-70% of patients, and it may be the sole manifestation of disease in 20-30% of patients.

The refractory nature of the disease, and the potential of the lesion to become erosive, atrophic, or even carcinogenic, correlates with patient's poor quality of life because of the associated pain and discomfort. A study assessing DLQI (Balci and Inandi 2008), reported that patients with lichen planus describe the impact of the disease on the quality of life comparably to patients with psoriasis.

Histologically, the disease shows apoptosis of keratinocytes, acanthosis, hypergranulosis, vacuolating degeneration of the basal layer of the epithelium and a lymphocytoid, cell-rich infiltrate in the upper dermis (Cassol-Spanemberg et al 2019). An important entity in the differential diagnosis of lichen planus are lichenoid drug reactions, which can be virtually indistinguishable from cutaneous lichen planus both clinically and histopathologically.

There are no established guidelines for lichen planus treatment, and as yet the pathogenesis and potential therapeutic targets of the disease remain poorly understood. Conventional therapies primarily aim at healing of erosive or atrophic lesions and relieving symptoms such as itch (CLP) or pain (MLP). Current clinical practice utilizes topical and systemic corticosteroids, retinoids, calcineurin inhibitors (such as cyclosporine, tacrolimus and pimecrolimus), and in some cases light therapy.

Topical corticosteroids have been utilized historically as first-line drugs, while systemic treatments are reserved for patients with disease that is more widespread, unresponsive to topical treatment or in case of acute exacerbations (Thongprasom and Dhanuthai 2008).

Despite the etiology of lichen planus being unclear, the abundance of the lymphocytic T cell infiltrate supports the participation of cellular immunity with both helper and cytotoxic T cells

playing a vital role in its pathogenesis. A delayed hypersensitivity immune reaction, in which the release of cytokines by activated T cells leads to the attraction of other immune cells and to the destruction of keratinocytes by cell-mediated cytotoxicity, has been implicated in the pathogenesis of lichen planus (Shaker and Hassan 2012).

Notably, every step mediated by T cells in the pathogenesis of lichen planus is amendable for interruption, and recent innovations in biologic therapies allows targeting several of these steps. In fact, several anecdotal cases have been described, providing evidence of therapeutic benefit for patients undergoing biologic therapies (Zhang et al 2011).

Recently, a case report showed the potential of biologic agents targeting the IL-23/Th17 axis to induce clinical remission and strong improvements on a cellular/molecular level in 5 patients with steroid refractory lichen planus (Solimani et al 2019), corroborating numerous previous findings and suggesting a key role for IL-17A in the pathogenesis of lichen planus. It also showed the presence of IL-17A producing Th17 as well as Tc17 cells in lichen planus lesions. In fact, several papers described elevated serum concentrations of IL-17A and increased numbers of peripheral and lesional Th17 cells in patients with mucocutaneous and oral lichen planus, as well as upregulation of IL-17A and Th17-derived cytokines (Schmidt et al 2018, Gueiros et al 2018).

Secukinumab (AIN457) is a recombinant high-affinity fully human monoclonal anti-human IL-17A antibody of the immunoglobulin (Ig) G1/κ-class. Secukinumab binds to human IL-17A and neutralizes the bioactivity of this cytokine. IL-17A is the central cytokine of a newly defined subset of inflammatory T cells, the Th17 cells which, , are pivotal in multiple autoimmune and inflammatory processes. IL-17A is mainly produced by memory effector CD4+ and CD8+ T lymphocytes and is recognized as one of the principal pro-inflammatory cytokines in immune mediated inflammatory diseases. Its neutralization is expected to treat the underlying pathophysiology of immune mediated disease, and as a consequence provide relief of symptoms.

Secukinumab (Cosentyx®) with a recommended dose of 300 mg was approved in 2014 in Japan, in 2015 in the US, EU and Switzerland for the treatment of moderate to severe plaque psoriasis in adults. Secukinumab is also approved for the treatment of adult patients with psoriatic arthritis or ankylosing spondylitis. Secukinumab is available as a powder for solution for injection, and as a solution of 150 mg in 1 mL for injection in pre-filled syringe or auto-injector.

The Investigator's Brochure (IB 2020) provides a more detailed review of the pre-clinical and clinical information on secukinumab.

Secukinumab has proven to be a suitable therapeutic option for immune mediated disorders, and based on the available scientific evidence and case reports, secukinumab has the potential to be an effective therapy for patients with moderate to severe lichen planus.

The aim of the present study is to assess the efficacy, safety, [redacted] and tolerability of two dose regimens of secukinumab in patients with moderate to severe lichen planus.

1.2 Purpose

The purpose of this proof-of-concept study is to elucidate the efficacy of secukinumab in the treatment of adult patients with biopsy-proven lichen planus not adequately controlled by topical therapies, and to assess the safety and tolerability over 32 weeks.

Lichen planus (LP) is a chronic, inflammatory condition affecting different locations of the body (skin, oral cavity, genitalia, scalp, and nails), sometimes concomitantly.

Current therapies used for lichen planus are mostly symptomatic and utilizes wide-spectrum immunosuppressive or anti-inflammatory topical or systemic agents. However, 30-50% of patients are refractory to current therapies and experience a higher burden of disease due to lack of clinical control, as well as significant psychological discomfort and social disability resulting in profoundly impaired quality of life.

These patients may benefit from a systemic, targeted therapy selectively inhibiting IL-17A, a key player in the skin inflammatory cascade. This study will evaluate the therapeutic efficacy of secukinumab in treating three well-defined subtypes of lichen planus, for which no systemic therapy is currently approved and which could be eligible for treatment with secukinumab.

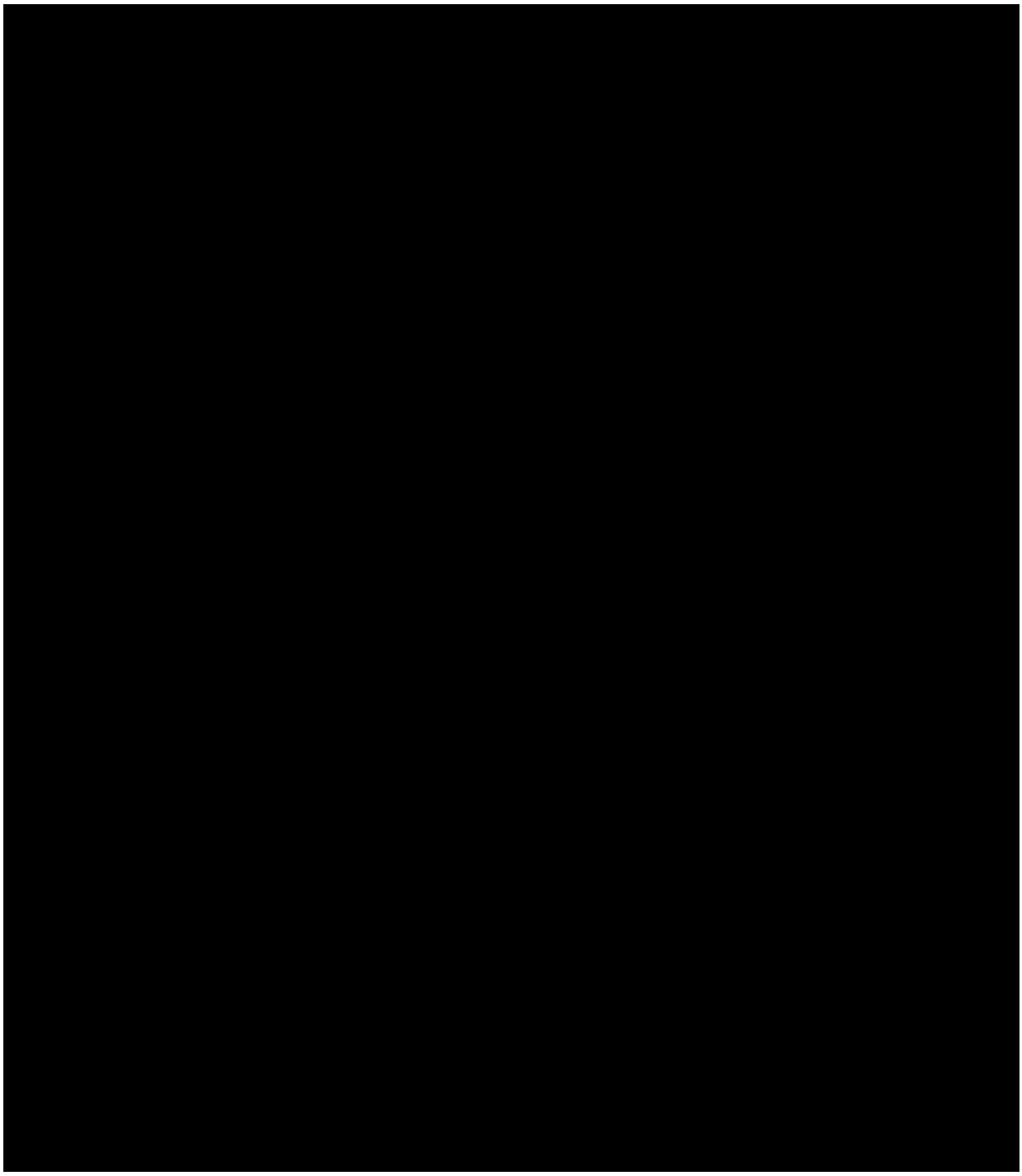
2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate the clinical efficacy of secukinumab 300 mg every 4 weeks (Q4W) in subjects with cutaneous lichen planus (CLP), mucosal lichen planus (MLP), or lichen planopilaris (LPP) inadequately controlled by topical therapies, with respect to improvement in Investigator's Global Assessment (IGA) score by Week 16, compared to placebo.	• Achievement of IGA response at Week 16 *Patients diagnosed with biopsy-proven forms of CLP, MLP or LPP will be considered responders if they achieve an absolute IGA score ≤2 at Week 16*
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• The secondary objectives of this trial comprise the following: - evaluate the efficacy of secukinumab 300 mg Q4W compared to placebo throughout 16 weeks in Treatment Period 1; - evaluate the long term efficacy of secukinumab 300 mg Q4W throughout 32 weeks in Treatment Period 2; - evaluate the efficacy of secukinumab 300 mg Q2W in Treatment Period 2; - evaluate the safety profile of secukinumab 300 mg throughout the duration of the study. Detailed assessments are described the next section.	
All subtypes Investigator's Global Assessment (IGA)	• Achievement of 2 points improvement in the IGA score from baseline to Week 16 and 32, and throughout the duration of the study Achievement of IGA 0/1 at Week 16 and 32, and throughout the duration of the study

Objective(s)	Endpoint(s)
• Dermatology Life Quality Index (DLQI)	• Absolute and relative change in DLQI from baseline to Week 16 and 32, and throughout the duration of the study Achievement of DLQI 0/1 score at Week 16 and 32, and throughout the duration of the study
• Patient assessment of itch (NRS)	• Absolute and relative change in NRS from baseline to Week 16 and 32, and throughout the duration of the study
• Patient assessment of pain (NRS)	• Absolute and relative change in NRS from baseline to Week 16 and 32, and throughout the duration of the study
• To assess the safety and tolerability of secukinumab in subjects with lichen planus.	• Adverse events, laboratory values, vital signs
Cutaneous Lichen Planus (CLP)	
• Physician Assessment of Surface Area of Disease (PSAD) for Skin Disease	• Absolute and relative change in PSAD from baseline to Week 16 and 32, and throughout the duration of the study
Mucosal Lichen Planus (MLP)	
• Reticular Erythematous Ulcerative (REU) score	• Absolute and relative change in REU score from baseline to Week 16 and 32, and throughout the duration of the study
• Oral Lichen Planus Symptoms Severity Measure (OLPSSM) score	• Absolute and relative change in OLPSSM score from baseline to week 16 and 32, and throughout the duration of the study
Lichen Planopilaris (LPP)	
• LPP Activity Index (LPPAI)	• Absolute and relative change in LPPAI score from baseline to Week 16 and 32, and throughout the duration of the study
• SCALPDEX Questionnaire	• Absolute and relative change in SCALPDEX Questionnaire score from baseline to Week 16 and 32, and throughout the duration of the study

[redacted]



3 Study design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial assessing the efficacy and safety of secukinumab 300 mg in two different dosing regimens in patients with biopsy-proven forms of lichen planus.

The study consists of three cohorts (one cohort per lichen planus subtype: cutaneous lichen planus (CLP), mucosal lichen planus (MLP) and lichen planopilaris (LPP)) and 4 study periods as illustrated in Figure 3-1.

Patients are assigned to one of the three cohorts based on their **predominant** subtype and undergo a biopsy to confirm the clinical diagnosis at the screening visit:

- **Predominantly cutaneous** lichen planus
- **Predominantly mucosal** lichen planus
- **Lichen planopilaris**

Each cohort will follow the same study design across the 4 periods:

- **Screening Period**: up to 4 weeks prior to baseline
- **Treatment Period 1**: baseline to Week 16
- **Treatment Period 2**: Week 16 to Week 32
- **Follow-up**: 8 weeks after Week 32

Screening period:

A screening period of up to 4 weeks is used to assess patient´s eligibility for the trial and to washout/adjust prohibited medications. The screening period covers the time from the signature of informed consent/screening visit (-4 weeks) to the randomization visit (Week 0).

Patients can be re-screened if the patient fails the initial screening due to a transient condition (not related to LP) or due to an insufficient prohibited medication washout period. Subjects can be re-screened only once and no re-screening procedure should be performed prior to re-consenting the subject. Patients may also be rescreened at a later time if site closures or other logistical issues prevent randomization as planned. Patients presenting with a reduction in the IGA score between screening and baseline, with the IGA not qualifying as moderate or severe at the baseline visit (i.e., IGA score of 2, 1 or 0), will not be eligible for re-screening.

Treatment Period 1:

Treatment Period 1 is placebo-controlled and covers the time from Week 0 (randomization visit) to Week 16. Patients who meet all eligibility criteria are randomized in a 2:1 ratio to one of the following two treatment arms **within** their cohort:

- **Secukinumab 300 mg every 4 weeks arm**: subjects receive a weekly induction treatment followed by secukinumab 300 mg every 4 weeks.
- **Placebo for 16 weeks followed by secukinumab 300 mg every 2 weeks arm:** subjects receive matching placebo injections.

Thirty-six patients will be randomized per cohort, 24 to active and 12 to placebo treatment, which means that the study will enroll approximately 108 subjects in total.

In Treatment Period 1 all subjects receive weekly subcutaneous injections of blinded study drug (either 300 mg secukinumab or placebo) at weeks 0, 1, 2, 3 and 4. Thereafter the frequency of blinded study drug injections for all subjects is every 4 weeks up to Week 16. Home administration of study drug is **not** allowed during Treatment Period 1. Subjects who complete Treatment Period 1 roll over to Treatment Period 2 at the week 16 visit. The only exception are subjects from the placebo for 16 weeks followed by secukinumab 300 mg every 2 weeks arm,

who achieve spontaneous remission at the Week 16 visit. Spontaneous remission is defined as an IGA of 0 or 1 at Week 16. These subjects do **not** proceed to Treatment Period 2 to avoid unnecessary treatment. Instead they will directly enter the Follow-up Period after the Week 16 visit.

Treatment Period 2:

Treatment Period 2 starts at the Week 16 visit and covers the time until the Week 32 visit.

Depending on the treatment arm, subjects receive the following treatments:

- **Secukinumab 300 mg every 4 weeks arm**: subjects receive continued treatment with secukinumab 300 mg every 4 weeks plus matching placebo injections to maintain treatment blinding.
- **Placebo for 16 weeks followed by secukinumab 300 mg every 2 weeks arm**: subjects are switched to active treatment with secukinumab 300 mg **every 2 weeks** including an induction starting at Week 16, with the exception of subjects achieving remission by Week 16.

The Week 16 injection is the first injection of Treatment Period 2.

Treatment remains blinded during Treatment Period 2. This means that, starting at the Week 16 visit, all subjects receive an induction consisting of weekly blinded study drug injections (either secukinumab 300 mg or placebo) at weeks 16, 17, 18, 19 and 20, followed by blinded study drug injections every 2 weeks, either secukinumab 300 mg alternating with placebo every 2 weeks (secukinumab 300 mg every 4 weeks arm) or secukinumab 300 mg every 2 weeks (placebo for 16 weeks followed by secukinumab 300 mg every 2 weeks arm) until week 30.

The last study drug injection is administered at Week 30. The end of Treatment Period 2 is Week 32. After Week 32, all subjects enter the Follow-up Period.

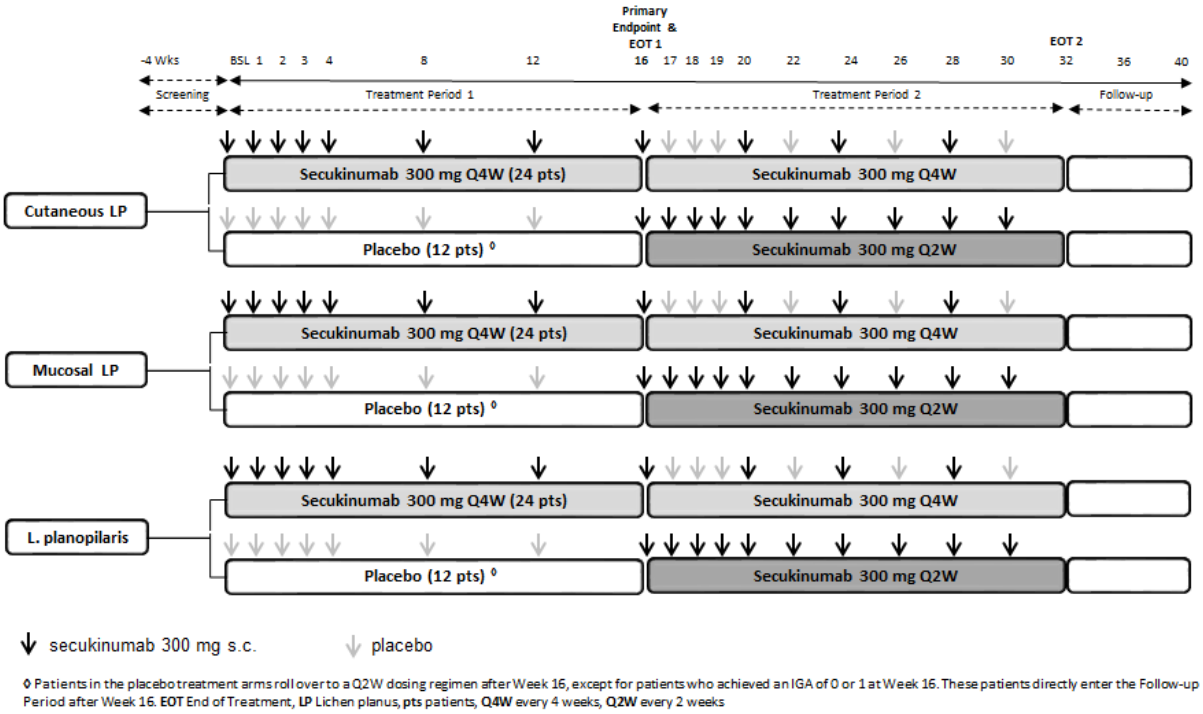
Subjects who discontinue study treatment prematurely for any reason other than withdrawal of informed consent should **not** be considered as discontinued from the study. Subjects should continue attending planned site visits and perform study assessments until the last visit of the treatment period during which they discontinue (Week 16 or Week 32).

Subjects, whether they are willing to continue attending further study visits or not, should attend the End of Treatment visit (EOT) of the study period during which they discontinued (EOT 1 for discontinuation during Treatment Period 1 and EOT 2 for discontinuation during Treatment Period 2). EOT1 should be performed 4 weeks after last dose of study, EOT2 should be performed 2 weeks after last dose of study drug. See Section 9.1 for further details.

Follow-up:

There is an 8-week Follow-up Period after Week 32. The End of Study is reached at Week 40. If a subject discontinues study during Follow-up period, visit Week 40 has to be performed.

Figure 3-1 Study design



◊ Patients in the placebo treatment arms roll over to a Q2W dosing regimen after Week 16, except for patients who achieved an IGA of 0 or 1 at Week 16. These patients directly enter the Follow-up Period after Week 16. **EOT** End of Treatment, **LP** Lichen planus, **pts** patients, **Q4W** every 4 weeks, **Q2W** every 2 weeks

4 Rationale

4.1 Rationale for study design

The double-blind, parallel, randomized, placebo-controlled design of this trial enables the evaluation of the efficacy and safety of secukinumab 300 mg in two different dosing regimens in three selected subtypes of lichen planus in an adequate and controlled setting.

The rationale to assign the subjects to subtype-specific cohorts and to monitor them in a parallel-group fashion is to assess the efficacy and safety of secukinumab in each subtype individually, using subtype-specific assessments and scores. There is broad pathophysiological overlap between the three selected subtypes (e.g. dominant role of T cells, presence of Th17 and Tc17 cells, overexpression of IL-17A in lesions in an encouraging case report on the use of secukinumab in lichen planus; Solimani et al 2019) giving strong evidence for a role of IL-17A in the pathophysiology of all three subtypes. Furthermore, there is broad clinical overlap between the three subtypes, especially between CLP and MLP subtypes, with many patients presenting concomitant symptoms and lesions. At the same time each subtype presents at different anatomical regions and with distinct clinical features and symptoms, e.g. ulceration can be present in the mucosal subtype but not in the cutaneous, whereas itching is highly relevant in patients with CLP but not in patients with MLP, or hair follicle inflammation, which is the unique feature of LPP. Patients are divided into three cohorts, according to their **predominant** clinical subtype in order to apply subtype-specific assessments. By using this design the trial is also able to collect data on the **non**-predominant ("concomitant") subtype, e.g. data on cutaneous lesions in a patient who is enrolled in the predominantly mucosal lichen

planus cohort. This ensures optimal usage of all available patient data. Since clinical sites with a special focus on the treatment of lichen planus usually see patients of all 3 selected subtypes, it also offers an operational advantage for sites to have the opportunity to enroll patients of all subtypes in one bundled trial. In addition, this "basket trial" approach enables pooled efficacy and safety assessment across all three subtypes.

The randomization process ensures a comparable and balanced profile of patients across treatment arms. The reason to have a 2:1 randomization favoring active treatment in Treatment Period 1 is to give more patients the opportunity to receive active treatment with secukinumab 300 mg every 4 weeks initially, during the first 16 weeks of the trial. Due to the convincing preclinical and initial clinical evidence outlined in the background section, the likelihood for efficacy of secukinumab in lichen planus is high. Moreover, there is no scientific evidence that would suggest that the safety profile of secukinumab in patients with lichen planus differs from the favorable safety profile observed in the extensive safety database of secukinumab in the currently approved indications (psoriasis, psoriatic arthritis and ankylosing spondylitis).

Treatment Period 1 has a placebo-controlled, double-blind design and a duration of 16 weeks. The rationale for this is that it allows the assessment of the efficacy and safety of secukinumab 300 mg in the three selected subtypes in comparison to placebo in an adequate setting. Week 16 represents a widely used and well-accepted timing for the assessment of the primary endpoint in secukinumab clinical trials in several inflammatory skin diseases such as psoriasis, hidradenitis suppurativa or atopic dermatitis. Standards for the timing of the assessment of the primary endpoint are not yet well established for clinical research in lichen planus, however, other trials conducted in this field have used comparable durations: Hazra et al. compared systemic betamethasone to methotrexate for 12 weeks (Hazra et al 2013), or enoxaparin was compared to methotrexate for 24 weeks (Lunge et al 2016).

During Treatment Period 2, subjects who have been on active treatment in Treatment Period 1 receive continued active treatment in the same dosing regimen (secukinumab 300 mg every 4 weeks) until Week 32. This allows the collection of longer term efficacy and safety data beyond 16 weeks of treatment. Subjects who have been on placebo treatment in Treatment Period 1 are switched to active treatment with secukinumab 300 mg every 2 weeks (starting with the regular weekly induction). This enables placebo treated patients to receive active treatment during the trial as well. Furthermore it allows the assessment of efficacy and safety of the 2-weekly dosing regimen in lichen planus. Subjects randomized to the placebo arm who achieve spontaneous clinical remission, which is defined as an IGA of 0 or 1, do not roll over to Treatment Period 2, instead they directly enter the Follow-up Period. The rationale for this is to avoid unnecessary treatment for these patients in Treatment Period 2. An IGA of 0/1 means that there is no or only minor disease activity left, and therefore, no need for a systemic treatment. This design may lead to partial unblinding, since patients who continue into Treatment Period 2 despite having achieved remission by week 16 will be known to have been on active treatment during Treatment Period 1. However, considering the benefit this design brings for placebo-treated patients with spontaneous remission and the fact that this is an early, proof-of-concept study, this limitation can be considered as acceptable.

The secukinumab 300 mg every 4 weeks dosing regimen is given to subjects in the active treatment arm in Treatment Period 1, while the higher dosing regimen, secukinumab 300 mg every 2 weeks, is explored in Treatment Period 2 in subjects switching over from placebo. This

design enables every participating subject to receive active treatment and makes the trial efficient by testing the secukinumab every 4 weeks dosing regimen versus placebo, while additionally giving the opportunity to explore the higher dosing regimen, secukinumab 300 mg every 2 weeks, without having to add an additional treatment arm.

Treatment blinding is maintained beyond the primary endpoint (week 16) throughout Treatment Period 2, which enables cross-comparison of the sequential efficacy and safety data of the 2-weekly dosing regimen in Treatment Period 2 to the 4-weekly dosing regimen in Treatment Period 1. Furthermore, it ensures that investigators remain blinded regarding the treatment subjects received during Treatment Period 1. In addition, continued blinding ensures more objective efficacy and safety assessment during Treatment Period 2.

An 8-week follow-up period will enable the assessment of disease activity [redacted] after the end of treatment.

The regular assessments of disease activity and clinical status ensure that safety is monitored closely and that both, subjects and investigators, have the opportunity to assess if the continued participation in the trial is to the patient´s benefit. If the subject´s participation is deemed not to be of benefit for the subject, she/he can exit the trial at any time.

4.2 Rationale for choice of background therapy

Patients entering the trial will be allowed to use topical therapies (low-moderate potency corticosteroids, Over the Counter (OTC) emollients and lubricants or mouthwash for pain; please see Section 6.2.1 for details) as background treatment in both arms. The primary reason for this is to alleviate the symptom burden of subjects receiving placebo treatment during the first 16 weeks of the study. Especially in patients with mucosal/ oral lichen planus, symptoms caused by oral ulcerations may be severe and therefore symptomatic background therapy (topical corticosteroids, local anesthetics etc.) is important for the adequate management of these patients. The allowed background treatments are typically used in clinical practice to treat lichen planus symptoms (Husein-ElAhmed et al 2019; Tziotzios et al 2018; Le Cleach and Chosidow 2012) (see Section 6 for details). Although it is a key inclusion criterion for patients to be inadequately controlled by topical treatments, this does not mean that the patients do not benefit from topical treatments at all. The allowed topical treatments still alleviate patients´ symptoms to a certain degree and may limit further progression of the disease.

[redacted]

[redacted]

[redacted]

4.4 Rationale for choice of control drugs

In this Phase 2 trial secukinumab 300 mg every 4 weeks is compared to placebo treatment in Treatment Period 1. This minimizes the number of patients that need to be enrolled in the trial, since an active comparator would reduce the assumed difference in efficacy between the two treatment arms significantly and thereby increase the number of patients required to statistically demonstrate this difference. The number of potential active comparators for this patient population is highly limited and so is the clinical evidence supporting them. Currently there are no approved treatment options specifically for this indication. Patients enrolling in this trial have moderate to severe lichen planus inadequately controlled by topical therapies. In this "second line" setting, systemic treatments are indicated. However, there are very few systemic treatments having proven clinical efficacy and safety in adequately powered, randomized, controlled trials. Systemic corticosteroids, retinoids, cyclosporin, methotrexate or hydroxychloroquine are options, but often characterized by limited efficacy and safety profiles that are far from optimal (Thandar et al 2019).

To minimize patients´ burden, the duration of placebo treatment is limited to 16 weeks and topical treatments including emollients, local anesthetics or corticosteroids of low to moderate potency are allowed as background therapy in both arms (see Section 6.2.1 for details). Although it is an inclusion criterion of this trial to be inadequately controlled by topical

treatments, this does not mean that patients do not derive any benefit from topical treatments. The allowed topical treatments while not fully curing the disease, still alleviate patients´ symptoms to a certain degree and may prevent further worsening of the disease that might occur without them. Continued topical treatment for 16 weeks is not considered a major safety risk for this patient population. Furthermore, randomization is done in a 2:1 ratio to reduce the number of patients under placebo treatment. After Week 16, all patients originally randomized to placebo, except those with spontaneous remission, are switched to active treatment with secukinumab 300 mg every 2 weeks, so all patients entering the trial receive active treatment, either starting at baseline or at Week 16. Since patients switching from placebo to active treatment are receiving secukinumab 300 mg every 2 weeks in Treatment Period 2, and patients who started with active treatment in Treatment Period 1 receive secukinumab 300 mg every 4 weeks throughout both treatment periods, the **cumulative** dose of secukinumab each patient population receives differs by only 10% (3300 mg for patients initially randomized to active treatment vs. 3000 mg for patients initially randomized to placebo). Furthermore if the patient´s participation in the trial is not considered to be of benefit for the patient by the investigator or the patient her-/himself, or the patient requires a different therapy than the one offered in the trial, she/ he can exit the trial at any time.

4.5 Purpose and timing of interim analyses/design adaptations

A primary endpoint analysis is planned to be conducted either once all patients have completed the Week 16 visit or once all patients of one of the 3 subgroups have completed the Week 16 visit. This will be decided depending on the recruitment of the 3 cohorts. The purpose of this primary endpoint analysis is to assess whether secukinumab shows efficacy and safety in the selected lichen planus subtypes at an early time point (proof of concept). This enables planning of further clinical development of secukinumab in lichen planus. At the end of the study, the final analysis of all data collected will be performed once all patients have completed their last study visit. All patients, investigators and site personnel will remain blinded until final database lock.

Further analyses are currently not planned. However, an unscheduled analysis could be conducted if a compelling reason arises, for example, if requested by health authorities.

4.6 Risks and benefits

Secukinumab has demonstrated a positive benefit-risk ratio in the treatment of multiple, chronic inflammatory conditions including moderate to severe plaque-psoriasis, psoriatic arthritis and ankylosing spondylitis. Based on the currently available preclinical as well as first clinical evidence (case series by Solimani et al 2019), IL-17A plays a key role in the pathophysiology of lichen planus and secukinumab, which is directed against IL-17A, therefore has the potential to reduce disease activity and improve symptom severity in patients with lichen planus.

Moreover, given the extensive exposure and the well-established and favorable safety profile of secukinumab in patients with moderate to severe plaque-psoriasis, Novartis is not aware of any medical/scientific evidence that would indicate potential differences in the safety profile of secukinumab between the psoriasis and the lichen planus patient populations.

Secukinumab´s currently approved dosing (300 mg given every 4 weeks) showed a consistent and favorable safety profile across a large clinical development program and extensive post-

marketing experience since its first approval for moderate to severe plaque-psoriasis in 2015. Approximately 4,000 patients with moderate to severe plaque-psoriasis were included in the studies of the registration program. This included 3,430 subjects treated with secukinumab in 10 phase II/III studies, 2,727 of whom were treated for at least 6 months and 2,029 of whom were treated for at least 48 weeks. Details of the risks and benefits are outlined in the current version of the Investigator's Brochure. The safety data from the completed and ongoing studies including AE and SAE data, laboratory parameters and immunogenicity data demonstrate a favorable safety profile. Observed risks include infections, in particular, upper respiratory tract infections, neutropenia and hypersensitivity reactions that can be seen with administration of foreign proteins. Most of the infections were non-serious, mild to moderate in severity, clinically easily manageable and did not lead to treatment discontinuation. Cases of neutropenia were uncommon, generally mild to moderate and transient and did not lead to treatment discontinuation, and only a few cases were temporally associated with non-serious infections. Subjects with pre-existing malignancies within the past 5 years are generally excluded from studies with secukinumab although there is no scientific basis to suggest that secukinumab would increase the risk for malignancies.

Secukinumab 300 mg s.c. given every 2 weeks is a non-approved dosing regimen currently. It has been administered in six completed studies in approximately 260 patients with psoriasis and uveitis, with approximately 120 patients receiving continuous treatment for at least 24 weeks. Furthermore the 300 mg every 2 weeks dosing regimen is currently being evaluated in two Phase 3 trials in patients with hidradenitis suppurativa (NCT03713632, NCT03713619) and in a Phase 3 trial in patients with moderate to severe plaque-psoriasis and a body weight ≥ 90 kg (NCT03504852). The safety profile observed in the data available to date is consistent with the known safety profile of secukinumab and no new safety concerns have been identified. Furthermore, secukinumab has been administered intravenously at a dose of 10 mg/kg body weight either short- or long-term in a number of clinical studies that enrolled patients with psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis or multiple sclerosis. The majority of patients was receiving 3 doses of 10 mg/kg i.v. over 1 month (Weeks 0, 2 and 4) and 38 patients with multiple sclerosis were receiving monthly 10 mg/kg i.v. doses for at least six months. Chronic, monthly treatment with secukinumab 10 mg/kg i.v. results in a monthly exposure that is approximately 2-fold higher compared to 300 mg s.c. every 2 weeks dosing (the bioavailability of secukinumab administered subcutaneously is 73%). No new or changed safety risks were observed with chronic i.v. treatment compared to the known safety profile of secukinumab with the approved doses. Comparisons across indications are valid given there are no clinically relevant differences in the pharmacokinetic profile of secukinumab observed between the various immune-mediated diseases studied (psoriasis, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, multiple sclerosis, Crohn’s disease, non-infectious uveitis). Additional information can be found in the IB for secukinumab.

The risk to subjects in this trial is also minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not enter or continue in the study.

The highly bothersome symptoms of pain or severe itching (Welz-Kubiak et al 2017), the significant impact moderate to severe lichen planus has on patient's quality of life including depression (Radwan-Oczko et al 2018; Cheng et al 2017; Welz-Kubiak et al 2017) and the very limited availability of effective and safe systemic treatment options for these patients inadequately controlled by topical treatments lead to a high degree of unmet medical need in the treatment of lichen planus. The established and favorable safety profile of secukinumab in moderate to severe plaque-psoriasis and the potential of secukinumab to reduce disease activity and improve symptom severity in patients with lichen planus, suggest that participation in this trial offers a well justifiable benefit-risk profile.

5 Population

Approximately 108 subjects with biopsy-proven lichen planus will be randomized in the study and assigned to 3 cohorts according to their predominant lichen planus subtype (predominantly cutaneous lichen planus, predominantly mucosal lichen planus or lichen planopilaris).

Each cohort will enroll 36 patients randomized in a 2:1 ratio (24 patients will enter the active arm, 12 patients the placebo arm).

Drop-outs after randomization will not be replaced.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Female and male patients ≥ 18 years of age.
3. Subjects must have biopsy-confirmed forms of cutaneous lichen planus (CLP), mucosal lichen planus (MLP), or active lichen planopilaris (LPP) eligible for systemic therapy based on the following criteria:
   - rated IGA of ≥ 3 at screening and baseline (moderate or severe) **AND**
   - inadequate response to topical corticosteroids of high-ultrahigh potency in the opinion of the investigator.
4. If using any of the allowed topical treatments on the affected areas, the dose and application frequency should remain stable for 2 weeks prior to randomization and until Week 16.

5.2 Exclusion criteria

Subjects meeting **any** of the following criteria are not eligible for inclusion in this study.

1. Clinical history suspicious for lichenoid drug eruption.
2. Lichen planus pigmentosus.
3. Clinical picture or history suspicious of paraneoplastic mucosal lichen planus.
4. Subjects whose lichen planus is a predominantly bullous variant.
5. Mucosal LP of the oral cavity or gastrointestinal involvement requiring the patient to use parenteral nutrition or feeding tube.
6. Clinical picture of scarring alopecia **without** active inflammation.

7. Clinical picture of burnt-out cicatricial alopecia (alopecia of Brocque).
8. Patients diagnosed with frontal fibrosing alopecia (FFA) without active patches of LPP.
9. Clinical picture of LPP in patients who have already failed 3 or more systemic immunosuppressive or immunomodulatory agents (e.g. systemic steroids, hydroxychloroquine, cyclosporine, methotrexate and mycophenolate mofetil).
10. Currently enrolled in any other clinical trial involving any investigational agent or device.
11. Previous exposure to any other biologic drug directly targeting IL-17A or IL-17RA (e.g. secukinumab, ixekizumab or brodalumab) or IL-23/p19 (e.g. tildrakizumab, guselkumab, risankizumab).
12. Diagnosis of active infectious diseases of the skin, scalp or mucosa (for example bacterial, viral or fungal infections of the mouth) that may interfere with the assessment of the study disease or require treatment with prohibited medications.
13. Diagnosis of active inflammatory diseases of the skin, scalp or mucosa other than lichen planus that may interfere with the assessment of the study disease or require treatment with prohibited medications.
14. Presence of any other skin condition that may affect the evaluations of the study disease.
15. Underlying conditions (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal - e.g., Inflammatory Bowel Disease) and/or presence of laboratory abnormalities which in the opinion of the investigator significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy.
16. Current, severe, progressive or uncontrolled diseases that render the patient unsuitable for the trial, including any medical or psychiatric condition that, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
17. Ongoing use of ANY treatment prohibited by the protocol (for details, refer to Table 6-2.
18. Plans for administration of live vaccines during the study period or within 6 weeks before randomization.
19. Pregnant or nursing (lactating) women.
20. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g. in European Union (EU) 20 weeks).

    Contraception methods include:

    - Total abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy [with or without hysterectomy], total hysterectomy or tubal ligation at least six weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient.

- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps).
- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the informed consent form (ICF).

Note: Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks prior to enrollment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

21. History of recurrent bacterial infection (at least 3 major infections resulting in hospitalization and/or requiring intravenous antibiotic treatment within the past 2 years).
22. History of congenital or acquired immunodeficiency (eg, Common Variable Immunodeficiency [CVID]).
23. Hepatitis B surface antigen (HBsAg) positive or Hepatitis B core antibody positive at screening.
24. History of Human Immunodeficiency Virus (HIV) infection.
25. Hepatitis C antibody positive at screening unless viral load is 0.
26. Evidence of tuberculosis infection as defined by a positive QuantiFERON® TB-Gold test (QFT) at screening. Patients with a positive or indeterminate QFT test may participate in the study if a full tuberculosis work-up (according to local practice/guidelines) completed within 12 weeks prior to randomization, establishes conclusively that the patient has no evidence of active or latent tuberculosis.
27. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease, or basal cell carcinoma or actinic keratosis that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
28. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

6 Treatment

6.1 Study treatment

The following investigational drug and comparator will be supplied and appropriately labeled by Novartis:

- **Investigational drug:** Secukinumab 300 mg, provided as 2 s.c. injections of 1 ml prefilled syringe (PFS). Each 1 ml syringe contains 150 mg secukinumab.
- **Comparator:** Placebo, provided as 2 s.c. injections of 1 ml prefilled syringe (PFS).

Each placebo pre-filled syringe contains a mixture of inactive excipients, matching the composition and the appearance of the secukinumab 150 mg dose.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Secukinumab 150mg	Solution for subcutaneous injection	Subcutaneous injection	Double blind supply, 1ml pre-filled syringe	Sponsor (global)
Placebo 150mg	Solution for subcutaneous injection	Subcutaneous injection	Double blind supply, 1ml pre-filled syringe	Sponsor (global)

Secukinumab and the secukinumab matching placebo will be labeled as "AIN457 150 mg / Placebo" (1 ml) to keep the blind. Subjects will initially be instructed on how to perform the injection by site staff. They will also receive written instructions as to how to self-inject using the pre-filled syringe.

Patients or caregivers not able/willing to self-administer the drug and perform home administration, will be allowed to return to the site for administration of the medication. During those visits, no additional assessments will be performed.

6.1.2 Additional study treatments

No other treatments beyond investigational drug, placebo and allowed concomitant topical treatments/background treatment are included in this trial.

6.1.3 Treatment arms/group

According to their diagnosis, subjects will be assigned at Screening visit to one of the following cohorts based on the **predominant** subtype of the disease (e.g. skin lesions are clinically dominant and the primary reason for treatment: patient is assigned to the cutaneous lichen planus cohort; mucosal lesions are clinically dominant and the primary reason for treatment: patient is assigned to the mucosal lichen planus cohort):

- **Cutaneous lichen planus**

- **Mucosal lichen planus**
- **Lichen planopilaris**

Patients presenting with two concomitant subtypes of lichen planus (e.g. concomitant presence of skin and mucosal lesions) will be eligible to enter the trial provided the cohort assignment occurs following the predominant subtype.

Within each cohort patients will be randomized to one of the treatment arms in a 2:1 ratio:

- **Cutaneous lichen planus** (n=36)
  - Secukinumab 300 mg every 4 weeks (n=24)
  - Placebo for 16 weeks followed by secukinumab 300 mg every 2 weeks (n=12)
- **Mucosal lichen planus** (n=36)
  - Secukinumab 300 mg every 4 weeks (n=24)
  - Placebo for 16 weeks followed by secukinumab 300 mg every 2 weeks (n=12)
- **Lichen planopilaris** (n=36)
  - Secukinumab 300 mg every 4 weeks (n=24)
  - Placebo for 16 weeks followed by secukinumab 300 mg every 2 weeks (n=12)

Treatment is divided into 2 treatment periods:

Treatment Period 1: Week 0-16

- Patients in the active **secukinumab 300 mg every 4 weeks treatment arm** receive induction with secukinumab 300 mg s.c. at Weeks 0, 1, 2, 3, 4 and then secukinumab 300 mg s.c. every 4 weeks, meaning at Weeks 8 and 12.
- Patients in the **placebo for 16 weeks followed by secukinumab 300 mg every 2 weeks treatment arm** receive corresponding placebo injections s.c. at Weeks 0, 1, 2, 3, 4 and then every 4 weeks, meaning at Weeks 8 and 12.

Treatment Period 2: Weeks 16-32

- Patients in the active **secukinumab 300 mg every 4 weeks treatment arm** stay on secukinumab 300 mg every 4 weeks, meaning they receive secukinumab 300 mg s.c. at Weeks 16, 20, 24 and 28. In order to maintain the blinding they additionally receive placebo injections at Weeks 17, 18 and 19 as well as placebo injections at Weeks 22, 26 and 30.
- Patients from the **placebo with switch to secukinumab 300 mg every 2 weeks treatment arm** switch over to active secukinumab 300 mg every 2 weeks treatment. They receive a weekly induction with secukinumab 300 mg s.c. at Weeks 16, 17, 18, 19 and 20 and then secukinumab 300 mg every 2 weeks, meaning at Weeks 22, 24, 26, 28 and 30.

The first injection of Treatment Period 2 is given at Week 16. The last injection (secukinumab 300 mg or placebo) is given in both the treatment arms **at week 30**.

6.1.4 Treatment duration

The duration of treatment is 32 weeks, with the last injection being given at Week 30. Subjects may be discontinued earlier from treatment due to unacceptable toxicity, disease progression, or at the discretion of the investigator or the subject.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Patients entering the trial are not allowed to use any topical therapies as background treatment except the ones defined in this section. Permitted topical therapies are listed below and must be recorded in the case report form (CRF).

The medications listed below are allowed for use throughout the duration of the trial: **subjects should be on a stable dose and application frequency of topical treatments 2 weeks prior to randomization. Administration should remain stable regarding dose and application frequency during Treatment Period 1 (until Week 16)**, and it is strongly recommended to maintain it at a stable level during Treatment Period 2 (from Week 16 until Week 32).

The following topical treatments are allowed:

- **Low-moderate potency corticosteroids** (**Group IV, V, VI and VII** as per WHO definition):

  Desoximetasone cream, 0.05%
  Fluocinolone acetonide ointment, 0.025%
  Fludroxycortide ointment, 0.05%
  Hydrocortisone valerate ointment, 0.2%
  Triamcinolone acetonide cream, 0.1%
  Betamethasone dipropionate lotion, 0.02%
  Betamethasone valerate cream, 0.1%
  Fluocinolone acetonide cream, 0.025%
  Fludroxycortide cream, 0.05%
  Hydrocortisone butyrate cream, 0.1%
  Hydrocortisone valerate cream, 0.2%
  Triamcinolone acetonide lotion, 0.1%
  Betamethasone valerate lotion, 0.05%
  Desonide cream, 0.05%
  Fluocinolone acetonide solution, 0.01%
  Dexamethasone sodium phosphate cream, 0.1%
  Hydrocortisone acetate cream, 1%
  Methylprednisolone acetate cream, 0.25%
  Triamcinolone acetonide oral rinse, 0.1%

The paste formulation of a corticosteroid is considered of comparable potency to its ointment formulation if the concentration is the same. The gel formulation of a corticosteroid is considered of comparable potency to its lotion formulation if the concentration is the same.

- **OTC emollients, shampoos and lubricants for the treatment of itch and/or pain,** e.g. anti-itch lotions containing menthol, pramoxine or antihistamines
- **(Mixed) medication for the treatment of oral pain** (e.g., lubricants, OTC mouthwashes containing diphenhydramine, viscous lidocaine, antacid, nystatin or corticosteroids **of Group IV, V, VI and VII** as per WHO definition)

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

All other forms of topical treatments **for any of the 3 LP subtypes** are not allowed during the Screening and Treatment periods. All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled in the study must be recorded on the appropriate CRFs.

6.2.2 Prohibited medication

Use of any treatments displayed in the table below that could confound the efficacy assessment of the investigational drug is **NOT** allowed during the course of the study for **ANY** indication. All prohibited treatments should be washed out as shown in the table below. The investigator should instruct the subject to notify the study site about any new treatments. At the discretion of the investigator, if any use of a prohibited treatment presents an undue safety risk for the subject, the study treatment must be discontinued. If a live vaccination has to be administered, the study treatment must be discontinued. If a prohibited treatment is used during the study, the subject should discontinue the use of the prohibited treatment if he/she wishes to continue in the study. In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator.

Table 6-2 Prohibited medication

Medication	Washout period before randomization	Note
Ustekinumab	24 weeks	
Etanercept	4 weeks	
Biological agents targeting IL-17A or IL-17RA (e.g. ixekizumab, brodalumab)	No prior use allowed	
Biological agents targeting IL-23/p19 (e.g. guselkumab, risankizumab, tildrakizumab)	No prior use allowed	
Systemic, biological immunomodulating agents other than above (e.g. agents directed against TNFα such as adalimumab, infliximab, certolizumab)	12 weeks	

Medication	Washout period before randomization	Note
Systemic, non-biological immunomodulating treatments (e.g. methotrexate, apremilast, systemic corticosteroids, cyclosporine, cyclophosphamide, sulphasalazine, azathioprin, mycophenolate mofetil, dapsone, hydroxychloroquine)	4 weeks	
Finasteride, dutasteride	4 weeks	
PPARγ agonists (e.g. pioglitazone), naltrexone, doxycycline	4 weeks	
Systemic use of griseofulvin or itraconazole	4 weeks	
Retinoids	4 weeks	
Low-level light therapy	4 weeks	
Phototherapy (e.g. UVB)	4 weeks	
Photochemotherapy (e.g. psoralen and UVA (PUVA))	4 weeks	
Topical calcineurin inhibitors (cyclosporin, tacrolimus, pimecrolimus) or topical vitamin D analogues	4 weeks	
Topical corticosteroids of **high - ultrahigh potency** (**group I, II, III** as per WHO definition)	4 weeks	If patients require topical corticosteroids, they have to be switched to the **low - moderate potency** corticosteroids (group IV, V, VI and VII per WHO definition) given in Section 6.2.1. Subjects should be on a stable dose and application frequency of the low - medium potency corticosteroids 2 weeks prior to randomization. Administration should remain stable regarding dose and application frequency during Treatment Period 1 (until Week 16), and it is strongly recommended to maintain it at a stable level during Treatment Period 2 (from Week 16 until Week 32).
Topical phosphodiesterase 4 inhibitors (e.g. crisaborole)	4 weeks	
Intralesional corticosteroid injection	4 weeks	
Depot corticosteroid injection	6 weeks	

Medication	Washout period before randomization	Note
Live virus vaccinations	6 weeks	
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives, whichever is longer	

6.2.3 Rescue medication

Use of rescue medication is not permitted in this study. Regarding the use of topical corticosteroids during the study, please see previous (section 6.2.1 and section 6.2.2).

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No., as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

The investigator or his/her staff will contact the interactive recording technology (IRT) and provide the requested identifying information for the subject to register them into the IRT.

If the subject fails to be treated for any reason, the IRT must be notified within 2 days that the subject was not treated. The reason for not being treated will be entered on the appropriate eCRF.

6.3.2 Treatment assignment, randomization

At the baseline visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

All efficacy and safety assessments should be done prior to calling IRT.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

This is a double blind study. Subjects, investigator staff, persons performing the assessments, and clinical trial team (CTT) will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

(1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exceptions:

- Specific members whose role in trial conduct requires their unblinding (e.g., IRT, designated Unblinded Data manager (if needed))
- Global Clinical Supply
- Designated Novartis study team members involved in the primary endpoint analysis

(2) the identity of the treatments will be concealed by the use of study treatments that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

[redacted]

Unblinding will occur in the case of subject emergencies and at the conclusion of the study.

6.5 Dose escalation and dose modification

Study treatment dose adjustments are not allowed and interruptions are not permitted except as described in Section 6.5.1.

6.5.1 Dose modifications

Study treatment interruption is only permitted if, in the opinion of the investigator, a subject is deemed to be placed at a significant safety risk unless dosing is temporarily interrupted. In such cases, study treatment should be interrupted only during the time that this risk is present and ongoing. Study treatment can be restarted at the next scheduled visit after resolution of the safety risk. These changes must be recorded on the appropriate eCRF.

6.5.2 Follow-up for toxicities

There is no protocol-guided follow-up for toxicities. Safety monitoring and reporting for AEs and SAEs is described in Section 10.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

All doses of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page (visit specific and summary pages). For study treatment administration at home, the investigator must promote compliance by instructing the subject to administer the study treatment exactly as instructed and by stating that compliance is necessary

for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to administer the study treatment.

All study treatment dispensed and returned must be recorded in the Drug Accountability Log. Compliance will also be assessed and confirmed by a field monitor by drug accountability logs, by documentation and information provided by IRT and by the qualified site personnel that are responsible for treatment dispensation, administration and accountability. Cross-checks should be performed for home administrations (H) and empty medication outer packing and subject's returned PFS should be collected for compliance checks by field monitors. This information should be captured in the source document at each visit.

[redacted]

6.6.2 Recommended treatment of adverse events

Treatment for adverse events should follow general guidelines for standard-of-care and is at the discretion of the investigator or treating physician. There are no specific treatment recommendations for adverse events that may possibly occur in this trial. Refer to the Investigator's Brochure for adverse events related to secukinumab.

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name
- subject number

In addition, oral and written information must be provided to the subject on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Study drug **must** be discontinued after emergency unblinding.

The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any subjects whose treatment code has been broken inadvertently for any reason.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under the investigational and control drugs section. A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label). Immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

In the event of a major health care disruption (e.g., pandemic, epidemic) that limits or prevents on-site study visits, study drug may be shipped or provided directly to patients for home administration if needed. The shipment/provisioning will be for a maximum quantity covering a 4-month supply. In this case, regular phone calls (every 4 weeks or more frequently, if needed) will occur between the site and the patient for instructional purposes, safety monitoring and discussion of the patient´s health status until the patient can again visit the site.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable

6.7.2 Instruction for prescribing and taking study treatment

Secukinumab solution for s.c. injection or placebo secukinumab solution (active or placebo, respectively) will be provided in pre-filled syringes (PFS).

Each subject will receive one box per visit throughout the study. Each box will contain:

- two 1ml PFS of secukinumab 150 mg **OR**
- two 1ml PFS of secukinumab/placebo 150 mg

All study treatment kits assigned to the subject by IRT during the study will be captured in the IRT system.

The first study treatment administration will occur at the baseline/randomization visit after the inclusion/exclusion criteria have been confirmed and all scheduled study assessments have been performed. All study assessments, including completion of Patient Reported Outcomes (PROs) and blood withdrawal, should be completed prior to the self-injection of study treatment.

All doses of study treatment (secukinumab and/or placebo) will be self-administered by the subject/ trained caregiver either at the study site after the study assessments for the visits have been completed or at home.

The first use at baseline and the Week 1 assessments of the self-injection will take place in the context of an observed assessment under the supervision of one site staff member. At the baseline visit, subjects will be instructed by the site staff on how to self-inject via the pre-filled syringe (Instructions for Use (IFU) containing detailed information about self-administration of study treatment should be provided to each subject at the beginning of the study). After providing detailed explanations/instructions, subjects will then be asked to raise any questions. Thereafter, they will proceed with self-injection.

Home administrations (H) should be done at pre-defined visits (see Section 3). Home administration can be performed by the subject or trained caregiver. If the subject or caregiver is not able/confident to perform home administration, the subject will be allowed to return to the site for administration of the medication. However, during those visits no additional assessments will be required.

In case of a major health care disruption (e.g., pandemic, epidemic) that limits or prevents on-site study visits, home administration of the study drug is generally permitted. Home administration can be performed by the patient or a trained caregiver. Study participants or caregivers will be trained adequately on how to perform administrations of the study treatment, if not already trained. If the patient or caregiver is not trained for drug administration and cannot visit the site to undergo training, the site can consider providing suitable virtual training and oversight. A joint decision together with the patient or caregiver should be made as to whether this constitutes sufficient training and oversight.

During home administrations, subjects will be instructed to contact the investigator/site staff in case they are experiencing any AE/SAEs or have any concerns.

Administration

The study treatment solution must be injected in **non-affected** areas of the skin.

Pre-filled syringes should be kept at 2 to 8°C (36°F and 46°F), never be frozen, and should be protected from light. Prior to administration, the boxes containing the pre-filled syringes should be allowed to adapt to room temperature unopened for about 20 minutes before administration. Used PFS (if according to the regulatory needs of the respective countries) should be stored in the original boxes and returned at the next site visit for reconciliation

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about previously known common side effects of the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that, in order to participate in the study, they must adhere to the contraception requirements.

[redacted]

Declining to participate in these optional assessments will in no way affect the subject’s ability to participate in the main research study.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

8 Visit schedule and assessments

The assessment schedule (Table 8-1) lists all of the assessments and details when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits on the designated day or as close as possible to the original planned visit schedule. Missed or rescheduled visits should not lead to automatic discontinuation.

During the treatment periods, subjects may be seen at unscheduled visits, e.g., if they experience deterioration of lichen planus, or AEs that in the opinion of the investigator need intervention, or repeated laboratory testing. The assessment(s) performed at an unscheduled visit are at the investigator's discretion.

In the event of a major health care disruption (e.g., pandemic, epidemic) that limits or prevents on site study visits, regular phone calls (every 4 weeks or more frequently, if needed) will occur until the subject can again visit the site. Events qualifying for being reported in the CRF (e.g., AE, procedure) should be entered as appropriate. Special effort should be made to collect information related to EOT or End of study visits. If it is not feasible to conduct the EOT or the Week 40 visit on-site, phone calls should be attempted instead.

Subjects who prematurely discontinue study treatment for any other reason than withdrawal of informed consent should not be considered as discontinued from the study, see Section 9.1. **Special effort should be made to ensure that patients who prematurely discontinue study treatment during Treatment Period 1 attend all scheduled visits until including the Week 16 visit.**

Assessments should be completed in the following order:

1. Patient reported outcomes (e.g. DLQI).
2. Physician reported assessments (e.g. IGA, REU): **IGA should be done first**, before applying the other physician reported assessments (e.g. REU or LPPAI).
3. Study visit procedures (e.g. vital signs measurements, laboratory and [redacted] biopsy procedures).

[redacted]

Table 8-1 Assessment Schedule

Period	Screening	Treatment Period 1									Notes
Visit Name	**Screening**	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**EOT1**	
Visit Numbers[1]	**1**	**20**	**100**	**110**	**120**	**130**	**140**	**150**	**160**		
Days	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**Last dose + 4 weeks**	
Informed consent	X										X Assessment to be recorded in the clinical database or received electronically from a vendor S Assessment to be recorded in the source documentation only [1] Visit structure given for internal programming purpose only [3] For all patients in the CLP cohort. Additionally for patients in the MLP cohort who have a concomitant cutaneous affection. [4] For all patients in the MLP cohort who have an oral affection of the disease. Additionally for patients in the CLP cohort who have a concomitant oral affection. [5] For all patients in the LPP cohort. [6] For all patients in the MLP cohort who have an oral affection of the disease.
Demography	X										
Inclusion / Exclusion criteria	X	X									
Smoking history	X										
Lichen planus medical history	X										
Previous lichen planus therapies	X										
Other medical history	X										
Prior medications	X										
Concomitant medications	update as necessary										
Prior or concomitant non-drug therapies/procedures	update as necessary										
Adverse Events	update as necessary										
Vital Signs	X	X					X		X	X	
Body Height	X										
Body Weight	X	X				X	X	X	X	X	
Physical examination	S	S									
Hepatitis screen	X										
Tuberculosis test	S										
Investigator's Global Assessment (IGA)	X	X		X		X	X	X	X	X	

Period	Screening	Treatment Period 1								Notes
Visit Name	Screening	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	EOT1	
Visit Numbers[1]	1	20	100	110	120	130	140	150	160		
Days	-28 to -1	1	8	15	22	29	57	85	113	Last dose + 4 weeks	
Physician´s assessment of surface area of disease (PSAD)[3]		X		X		X	X	X	X	X	[7] Not to be done if EOT already happened [8] For all patients in the CLP cohort. [9] For all patients in the MLP cohort. [10] Optional [11] Historical biopsies are accepted IF THEY ARE NOT OLDER THAN 3 MONTHS BEFORE SCREENING VISIT and if the investigator is able to provide the stained slides to the central lab for digitalization.
Reticular Erythematous Ulcerative (REU) score[4]		X		X		X	X	X	X	X	
Lichen Planopilaris Activity Index (LPPAI)[5]		X					X		X	X	
Oral Lichen planus symptom severity measure (OLPSSM)[6]		X		X		X	X	X	X	X	
SCALPDEX[5]		X				X	X	X	X	X	
DLQI		X				X	X	X	X	X	
[redacted]											
Patient assessment of itch		X		X		X	X	X	X	X	
Patient assessment of pain		X		X		X	X	X	X	X	
[redacted]											
Hematology	X	X					X		X	X	
Clinical chemistry	X	X					X		X	X	
Urine pregnancy test (local)	S	S							S[7]	S	
Pregnancy test (serum)	X										
[redacted]											

Period	Screening	Treatment Period 1									Notes
Visit Name	Screening	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	EOT1	
Visit Numbers[1]	1	20	100	110	120	130	140	150	160		
Days	-28 to -1	1	8	15	22	29	57	85	113	Last dose + 4 weeks	
Skin biopsy[8]	X[11]		[redacted]								
Mucosal biopsy[9]	X[11]										
Scalp biopsy[5]	X[11]										
Contact IRT	S	S	S[7]	S[7]	S[7]	S[7]	S[7]	S[7]	S[7]	S	
Drug administration		X	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]		

Period	Treatment Period 2											Notes
Visit Name	**Week 17**	**Week 18**	**Week 19**	**Week 20**	**Week 22**	**Week 24**	**Week 26**	**Week 28**	**Week 30**	**Week 32**	**EOT2**	
Visit Numbers[1]	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240**	**250**	**1999**		
Days	**120**	**127**	**134**	**141**	**155**	**169**	**183**	**197**	**211**	**225**	**Last dose + 2 weeks**	
Concomitant medications[2]	update as necessary											X Assessment to be recorded in the clinical database or received electronically from a vendor S Assessment to be recorded in the source documentation only [1] Visit structure given for internal programming purpose only [2] During home administrations, adverse events that may occur as well as concomitant medication should be collected by the investigator and reported in the eCRF [3] For all patients in the CLP cohort. Additionally for patients in the MLP cohort who have a concomitant cutaneous affection. [4] For all patients in the MLP cohort who have an oral affection of the disease. Additionally for patients in the CLP cohort who have a concomitant oral affection.
Prior or concomitant non-drug therapies/procedures	update as necessary											
Adverse Events[2]	update as necessary											
Vital Signs						X				X	X	
Body Weight				X		X		X		X	X	
Physical examination										S[7]	S	
Investigator's Global Assessment (IGA)				X		X		X		X	X	
Physician´s assessment of surface area of disease (PSAD)[3]				X		X		X		X	X	
Reticular Erythematous Ulcerative (REU) score[4]				X		X		X		X	X	
Lichen Planopilaris Activity Index (LPPAI)[5]						X				X	X	
Oral Lichen planus symptom severity measure (OLPSSM)[6]				X		X		X		X	X	
SCALPDEX[5]				X		X		X		X	X	
DLQI				X		X		X		X	X	
[redacted]												
Patient assessment of itch				X		X		X		X	X	
Patient assessment of pain				X		X		X		X	X	
[redacted]												

Period	Treatment Period 2											Notes
Visit Name	**Week 17**	**Week 18**	**Week 19**	**Week 20**	**Week 22**	**Week 24**	**Week 26**	**Week 28**	**Week 30**	**Week 32**	**EOT2**	
Visit Numbers[1]	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**240**	**250**	**1999**		
Days	**120**	**127**	**134**	**141**	**155**	**169**	**183**	**197**	**211**	**225**	**Last dose + 2 weeks**	
[redacted]												[5] For all patients in the LPP cohort.
Hematology						X				X	X	[6] For all patients in the MLP cohort who have an oral affection of the disease.
Clinical chemistry						X				X	X	
Urine pregnancy test (local)										S[7]	S	[7] Not to be done if EOT already happened.
Pregnancy test (serum)												
[redacted]												[8] For all patients in the CLP cohort.
Skin biopsy[8]												[9] For all patients in the MLP cohort.
Mucosal biopsy[9]												
Scalp biopsy[5]										X[7]	X	[12] These injections will be self-administered at home by the patient, unless a preference for office-administration is expressed
Contact IRT				S[7]		S[7]		S[7]		S[7]	S	
Drug administration				X[7]		X[7]		X[7]				
Home administration[12]	X[7]	X[7]	X[7]		X[7]		X[7]		X[7]			

Period	Follow-up		Unplanned	Notes
Visit Name	Week 36	Week 40	Unscheduled[13]	
Visit Numbers[1]			260	
Days	253	281	-	
Concomitant medications	update as necessary			X Assessment to be recorded in the clinical database or received electronically from a vendor S Assessment to be recorded in the source documentation only [1] Visit structure given for internal programming purpose only [3] For all patients in the CLP cohort. Additionally for patients in the MLP cohort who have a concomitant cutaneous affection. [4] For all patients in the MLP cohort who have an oral affection of the disease. Additionally for patients in the CLP cohort who have a concomitant oral affection. [5] For all patients in the LPP cohort. [6] For all patients in the MLP cohort who have an oral affection of the disease. [8] For all patients in the CLP cohort. [9] For all patients in the MLP cohort. [13] The assessments performed at an unscheduled visit are at the discretion of the investigator
Prior or concomitant non-drug therapies/procedures	update as necessary			
Adverse Events	update as necessary			
Vital Signs		X	X	
Body Height				
Body Weight		X	X	
Physical Examination			S	
Hepatitis screen				
Tuberculosis test			S	
Investigator's Global Assessment (IGA)	X	X	X	
Physician´s assessment of surface area of disease (PSAD)[3]	X	X	X	
Reticular Erythematous Ulcerative (REU) score[4]	X	X	X	
Lichen Planopilaris Activity Index (LPPAI)[5]		X	X	
Oral Lichen planus symptom severity measure (OLPSSM)[6]	X	X		
SCALPDEX[5]	X	X		
DLQI	X	X		
[redacted]				
Patient assessment of itch	X	X	X	
Patient assessment of pain	X	X	X	

Period	Follow-up		Unplanned	Notes
Visit Name	Week 36	Week 40	Unscheduled[13]	
Visit Numbers[1]			260	
Days	253	281	-	
[redacted]				
Hematology		X	X	
Clinical Chemistry		X	X	
urine pregnancy test (local)			S	
Pregnancy Test (serum)			X	
[redacted]				
Skin biopsy[8]				
Mucosal biopsy[9]				
Scalp biopsy[5]				
Contact IRT				

8.1 Screening

If for any reason the subject is a screen failure, the subject may be rescreened once only. If a subject rescreens for the study, t**hen the subject must sign a new ICF** and be issued a new subject number prior to any screening assessment being conducted for the subject under the new screening subject number. Patients may also be rescreened at a later time if site closures or other logistical issues prevent randomization as planned. Patients presenting with a reduction in the IGA score between screening and baseline, with the IGA not qualifying as moderate or severe at the baseline visit (i.e., IGA score of 2, 1 or 0), will not be eligible for re-screening. For all rescreened subjects, the investigator/qualified site staff will record if the subject was rescreened on the rescreening eCRF and the original screening number the subject was issued prior to the current screening number.

Informed Consent for a rescreened subject must be obtained prior to performing any study-related assessment or collecting any data for the Screening Visit. For rescreening, all screening assessments must be performed as per protocol, except for the tuberculosis (TB) **work up**, if applicable, if performed not more than 12 weeks before randomization. However, the subject must repeat the QuantiFERON-TB Gold assay performed by the central laboratory.

Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (Section 10.1.3, SAE reporting). Adverse events that are not SAEs will be followed up by the investigator and collected only in the source data. If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

8.2 Subject demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with the CRF.

8.2.1 Demography

Subjects demographics data will include: age, gender, race and ethnicity.

8.2.2 Prior Lichen Planus medical history and previous therapies

The following information should be collected and entered in the relevant CRF page:

- lichen planus subtype: Cutaneous lichen planus, mucosal lichen planus, lichen planopilaris (note that the predominant subtype as well as potential concurrent subtypes, if present, are collected) .
- date of first symptoms
- date of first diagnosis of lichen planus

- any treatments for lichen planus since initial diagnosis prior to study entry will be collected and recorded in the eCRF along with the duration of the prior therapy and reason for discontinuation.

8.2.3 Smoking history

The current and/or previous tobacco use will be recorded prior to randomization, as well as the estimated number of pack-years based on the approximate consumption per year. Use of e-cigarettes will be recorded in the Medical history CRF.

8.2.4 Medical history/current medical conditions

Relevant medical history and current medical conditions includes data prior to signing of the informed consent and should be recorded in the Medical History eCRF. Whenever possible, diagnoses and not symptoms should be recorded.

Significant findings that are observed after the subject has signed the ICF and that meet the definition of an AE must be recorded in the AE eCRF.

8.2.5 Prior and concomitant medications

Concomitant medications and prior medications taken over the 6 months preceding study enrollment for reasons other than lichen planus will be captured at the screening visit, and updated as necessary in the relevant eCRF.

8.2.6 Determination of the tuberculosis status

Determination of tuberculosis (TB) status should be done at Screening and should be performed as defined by local guidelines. The TB status must be determined by medical history, signs, symptoms, and TB testing (QuantiFERON-TB Gold assay). Any significant findings should be recorded in the eCRF (Section 15.3) for more details.

8.3 Efficacy

The following section describes the efficacy measures applied in this study. Whenever possible the following assessments should be performed by the same evaluator throughout the study.

8.3.1 Investigator's Global Assessment (IGA)

The IGA grading should be done first, before performing any other physician assessments (e.g. REU, LPPAI, etc). Whenever possible, the IGA assessment should be performed by the same evaluator throughout the study.

The IGA table (Table 8-2) will provide a harmonized, 5-point grading system to assess disease severity for patients of all 3 subtypes entering the study.

The predominant subtype defines the IGA score of the patient.

The IGA grading is based on the predominant subtype alone, meaning on the subtype of the cohort the patient is in. In addition, the IGA score is also collected **separately** for concomitant subtypes, if present.

Table 8-2 Investigator's Global Assessment grading

IGA score	***Cutaneous Lichen Planus***	***Mucosal Lichen Planus***	***Lichen Planopilaris***
0 - Clear	No disease. Possible flat, hyperpigmented lesions.	No disease.	No active disease. Hypopigmented, cicatricial patches. Pull test negative.
1 - Minimal	Barely palpable (<0.5 mm), scattered papules, mild erythema. Typically associated with minimal pruritus.	Reticular, white, patch-type striations involving any oral or genital mucosal site(s) ("Wickham Striae"). Absence of ulcers. Typically associated with no symptoms.	Predominantly inactive disease (hypopigmented cicatricial patches). Absence of disease spreading. Pull test negative. Minimal scalp erythema and/or perifollicular erythema without scale. Typically associated with minimal pruritus.
2 - Mild	Moderately elevated papules (<1 mm) and/or small plaques (<2 cm^2). Involvement of limited areas, erythema. Typically associated with mild pruritus.	Plaque-type, mucosal lichen planus involving any oral or genital mucosal site(s). Absence of ulcers or presence of one focal ulceration (<0.5 cm^2). Typically associated with mild pain or sensitivity.	Rare perifollicular erythema, rare perifollicular hyperkeratosis and interfollicular scale. Stable or slowly spreading disease. Pull test negative. Typically associated with mild pruritus.
3 - Moderate	Thick, elevated (<2 mm), hypertrophic, violaceous papules or presence of non-hypertrophic, plaque-like disease (>2 cm^2), either generalized or involving specific areas or specific locations (e.g. face, neck). Red/violaceous erythema, possible scales. Typically associated with moderate pruritus.	Desquamative gingivitis or vulvitis. Presence of unilateral or bilateral ulcerations involving any oral or genital mucosal site(s). Overall area affected by ulceration should be <2 cm^2. Typically associated with moderate pain and sensitivity.	Hairless patches with perifollicular and interfollicular erythema, follicular hyperkeratosis and interfollicular scaling. Active spreading disease. Pull test positive for telogen hairs. Typically associated with moderate pruritus, pain and/or burning.

4 - Severe	Generalized, papular or plaque-type, elevated lesions (>2 mm) OR localized hypertrophic lesions (>2 cm^2). Marked red/violaceous erythema. Possible scales, blisters and ulcers. Typically associated with severe pruritus.	Presence of bilateral or extensive unilateral ulcers involving any oral or genital mucosal site(s). Overall area affected by ulceration should be >2 cm^2. Possible esophageal involvement (established by endoscopy). Typically associated with severe pain and sensitivity.	Hairless patches with perifollicular and interfollicular, intense erythema, extensive perifollicular and interfollicular scaling. Crusting, pustules. Active spreading disease. Pull test positive for telogen or anagen hairs. Typically associated with severe pruritus, pain and/or burning.

The grading should be mainly driven by the lesion characteristics. Symptoms, such as pain or pruritus, may or may not be associated.

8.3.2 Physician´s assessment of surface area of disease (PSAD)

The Physician Assessment of Surface Area of Disease (PSAD) evaluates the extent of cutaneous lesions. Since no validated scales are available to quantify the area of disease in CLP, the present study will utilize the PSAD grading score as previously reported in the only randomized trial conducted with a biologic therapy in CLP (etanercept, NCT00285779).

The PSAD will be estimated by the investigator/trained qualified designee from the percentages of areas affected, including head, trunk, upper limbs and lower limbs. Whenever possible, the same assessor should perform the PSAD assessment at all visits. The assessor will report the percentage of the surface area involved with disease using a Likert scale.

Assessment scores range from 0-5, with lower scores corresponding to lower percentages of surface area with disease.

0: clear

1: <2% of the total body surface area. Small, localized papules

2: 2-9% of the total body surface area. Lesions affecting limited areas (e.g. wrists or ankles)

3: 10-29% of the total body surface area. Lesions affecting extensive areas (e.g. upper limbs or back)

4: 30-50% of the total body surface area. Lesions affecting extensive areas or in multiple locations (e.g. trunk and lower/upper limbs)

5: >50% of the total body surface area. Generalized involvement

As reference, the percentages utilized for the Body Surface Area (BSA) assessment should be considered (head=10%, trunk=30%, upper limbs=20%, lower limbs=40%).

Post-inflammatory hyperpigmentation should NOT be considered as surface area affected by the disease.

The PSAD assessment is required for all subjects enrolled in the CLP cohort. In addition, the PSAD assessment is required for subjects enrolled in the MLP cohort in case they have a **concomitant** cutaneous involvement.

8.3.3 Reticulations, erythema and ulcerations (REU) score

The reticulation, erythema and ulcerations score (REU score) was developed by Piboonniyom et al. as a semiquantitative scale for the assessment and monitoring of oral lichen planus as well as oral graft-versus-host disease (Piboonniyom et al 2005). It measures disease severity based on 3 dimensions: reticulation, erythema and ulceration. Whenever possible, the REU assessment should be performed by the same evaluator throughout the study.

The REU score is applied for all patients in the MLP cohort who have an **oral** presentation of the disease. In addition, the REU scoring is also done for patients in the CLP cohort in case they have a concomitant **oral** involvement.

The assessment is done as follows:

The oral cavity is divided into the following 10 sites:

- upper/lower labial mucosa
- right buccal mucosa
- left buccal mucosa
- dorsal tongue
- ventral tongue
- floor of mouth
- hard palate mucosa
- soft palate/tonsillar pillars
- maxillary gingiva
- mandibular gingiva

The severity of the lesions is scored for each site individually according to the presence of reticular/hyperkeratotic, erosive/erythematous and ulcerative lesions:

- **Reticulation:** reticular/hyperkeratotic lesions: 0 - 1
  - 0: no white striations
  - 1: presence of white striations or keratotic papules
- **Erythema:** erosive/erythematous lesions by area of involvement: 0 - 3
  - 0: no lesion
  - 1: lesions < 1 cm^2
  - 2: lesions 1 - 3 cm^2
  - 3: lesions > 3 cm^2
- **Ulceration:** ulcerative lesions by area of involvement: 0-3
  - 0: no lesion
  - 1: lesions < 1 cm^2
  - 2: lesions 1 - 3 cm^2

- 3: lesions > 3 cm^2

For each of the 3 clinical dimensions, a score is then derived by summation of the scores from all 10 oral cavity sites: Reticular score = ∑R, erythema score = ∑E, and ulcerative score = ∑U.

These 3 scores then add up to a **total weighted score: ∑R + ∑(E x 1.5) + ∑(U x 2.0).**

8.3.4 Lichen planopilaris Activity Index (LPPAI)

The LPPAI is a numeric score to quantify the signs and symptoms of LPP introduced by Chiang et al. (Chiang et al 2010). The LPPAI assesses symptoms (pruritus, pain, burning), signs (erythema, perifollicular erythema and scale), a measure of activity (pull test) and extension of disease. These subjective and objective measures are assigned numeric values to establish a disease activity score. Whenever possible, the LPPAI assessment should be performed by the same evaluator throughout the study. It is applied for subjects in the LPP cohort only.

Table 8-3 LPPAI

Symptoms	**Score**
Pruritus	0 - 3
Pain	0 - 3
Burning	0 - 3
Signs	
Scalp erythema	0 - 3
Perifollicular erythema	0 - 3
Perifollicular scale	0 - 3
Pull test	0 / 1 & anagen / total
Spreading	0 - 2

Score for signs and symptoms: 0=absent, 1=mild, 2=moderate, 3=severe

Score for anagen pull test: To conduct the anagen pull test grasp a small group of 10 - 20 hairs between the thumb, second and third finger at the scalp end of the hair shafts and pull away from the scalp with a slow, firm 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, **1** for the **presence** of anagen hairs) and as anagen hairs/total hairs pulled.

Score for spreading: 0 = no spreading, 1 = indeterminate, 2 = spreading. When the hair loss is difficult to judge, the issue of spreading is recorded as indeterminate.

The weights given to the symptoms (30%), signs (30%), anagen pull test (25%) and presence of spreading (15%) then lead to the final equation:

LPPAI (0-10) = (pruritus + pain + burning + scalp erythema + perifollicular erythema + perifollicular scale)/3 + 2.5x(pull test) + 1.5x(spreading/2)

8.3.5 Appropriateness of efficacy assessments

IGA: Using an IGA type of assessment represents the most widely used assessment strategy to evaluate patients' disease severity and improvement. It has been utilized as a primary endpoint in several clinical trials investigating psoriasis, and it is routinely used in clinical practice.

Available IGA scores are not adequate to assess disease severity in lichen planus, nor to describe the complex features of lichen planus. The IGA presented in this study has been developed with the contribution of the medical experts included in the Steering Committee, and describes the different stages of disease severity harmonizing the scores across the different subtypes of lichen planus. This represents the first attempt to develop a unified dermatologic score to assess disease severity in patients with lichen planus.

PSAD: the PSAD is a quantitative score describing the extent of the disease in patients with lichen planus. It is not a validated score: in fact, the paucity of RCTs conducted in patients with CLP led to the absence of standardized measurements to assess the severity of the disease. The only RCT conducted with a biologic therapy in this population (etanercept, NCT00285779) utilized this scale: as the disease localization can be different from other skin diseases (i.e. psoriasis), BSA may not be the preferred measurement. This study will elucidate the role of PSAD in the assessment of disease severity in lichen planus.

LPPAI: the LPPAI is a numeric score to quantify the signs and symptoms of LPP introduced by Chiang et al. (Chiang et al 2010). It is the only available disease-specific score for LPP and was used in a number of trials/case series to measure treatment efficacy in this indication (Naeini et al 2017; Fonda-Pascual et al 2018; Yang et al 2018)

REU: the reticulations, erythema and ulcerations score (REU score) was developed by Piboonniyom et al. as a semiquantitative scale for the assessment and monitoring of oral lichen planus as well as oral graft-versus-host disease (Piboonniyom et al 2005). It measures disease severity based on reticulations, erythema and ulceration. It is easy to use, offers a high intra as well as inter-observer reliability (Piboonniyom et al 2005; Gobbo et al 2017), correlates with pain and reliably reflects improvement attributable to treatment (Park et al 2012).

8.4 Safety/Tolerability

All blood draws and safety assessments should be done prior to study treatment administration. Appropriate safety assessments (e.g., evaluation of AEs and SAEs) should be repeated after the dose is administered.

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

In the event of a major health care disruption (e.g., pandemic, epidemic) that limits or prevents on-site study visits, regular phone will occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the patient´s health status until the patient can again visit the site. Events qualifying for being reported in the CRF (e.g., AE, procedure) should be entered as appropriate. If patients cannot visit the site to have urine pregnancy tests done, the urine pregnancy test kits can be provided to the patient or shipped directly to the patient's home (e.g., together with the study drug). After appropriate instruction, patients can perform the urine pregnancy test at home and report the result to the site. It is important that patients do the pregnancy test first and only if the test result is negative proceed with the administration of the study drug.

For details on AE collection and reporting, refer to Section 10.1.1.

Table 8-4 Assessments & Specifications

Assessment	Specification
Physical examination	A physical examination, including general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems will be performed as indicated in Table 8-1. If necessary, based on medical history and/or symptoms, additional exams will be performed at the discretion of the investigator. Whenever possible, assessments for an individual subject should be performed by the same member of the study site staff throughout the study. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs (including blood pressure and pulse measurements) will be assessed as indicated in Table 8-1. Whenever possible, assessments should be performed by the same study site staff member throughout the study. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured twice (measurements separated by 1 to 2 minutes) using an appropriate device, with a correctly sized cuff (Mancia 2007). In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Measurements will be recorded in the source documentation and the average of the two measurements will be entered on the Vital Signs eCRF section.

	Normal blood pressure will be defined as a systolic pressure of 90 to < 120mmHg, and a diastolic blood pressure of 60 to < 80 mmHg under measurement conditions as outlined above. Notable blood pressure will be hypertension (systolic ≥ 140 mmHg and/or diastolic > 90 mmHg) or hypotension (systolic < 90 mmHg and/or diastolic < 60 mmHg). A blood pressure indicative of pre-hypertension (systolic 120 to < 140 mmHg and/or diastolic 80 to < 90 mmHg) will **not** be regarded as notable (Chobanian et al 2003). A normal pulse rate will be defined as a rate of 60 to 100 bpm (beats per minute) under the measurement conditions outlined above. Notable pulse rates are a rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia). No specific action is pre-defined within this protocol to respond to specific abnormal vital signs, as it will be decided by the investigator whether and which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the subject.
Height and weight	Height and body weight will be measured as listed in Table 8-1. Height and body weight will be measured in indoor clothing, but without shoes. Whenever, possible, body weight assessments should be performed by the same study site staff member; the same scale should be used throughout the study.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed below, unless noted otherwise. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Refer to the Laboratory Manual for identification of laboratory reference range values and the schema for notification of site staff and Novartis for out of range values.

Subjects should avoid smoking within the hour preceding the blood draws. Appendix 1 (Section 15.1) shows the extended laboratory ranges that are considered clinically notable. No specific action is pre-defined within this protocol to respond to specific abnormal laboratory values, as it will be decided by the investigator whether and which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the subject.

The tests will be conducted as defined in the assessment schedule.

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

Chemistry	Albumin, Alkaline phosphatase, ALT, AST , Gamma-Glutamyl-Transferase (GGT), Lactate Dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Urea, Uric Acid, HbA1c, hs-CRP (will not be communicated to the site staff, incl. the investigator, or to Novartis during the study to maintain blinding)
Hepatitis Screening	Hepatitis screening will be conducted at the screening visit.
Pregnancy Test	Serum / Urine pregnancy test

8.4.2 Pregnancy

The study treatment must not be given to pregnant women; therefore, effective methods of birth control must be used for women of childbearing potential (see exclusion criteria definitions, Section 5.2).

A serum Human Chorionic Gonadotropin (β-hCG) test will be performed at Screening in all women of childbearing potential. In addition, local urine pregnancy tests must be performed as indicated in Table 8-1.

A positive urine pregnancy test must be followed by a serum β-hCG test aiming at confirming the result. Any woman with a confirmed positive pregnancy test during Screening is not eligible for randomization. A positive urine pregnancy test requires immediate interruption of study treatment until a serum test is performed and found to be negative. If the serum test is positive, the subject must be discontinued from the study treatment (see Section 9.1).

Additional pregnancy testing may be performed as per local requirements.

8.4.3 Appropriateness of safety measurements

The safety assessments selected are standard measures for clinical trials with a biologic, immunomodulating agent in dermatologic diseases.

8.5 Additional assessments

The following additional assessments will be applied in this trial:

- Patient Reported Outcomes (PROs)
- [redacted]

8.5.1 Patient Reported Outcomes (PROs)

The following PROs will be applied as specified in Table 8-1:

[redacted]

- Patient Assessment of Itch (NRS)
- Patient Assessment of Pain (NRS)
- Oral Lichen Planus Symptom Severity Measure (OLPSSM)
- Dermatology Life Quality Index (DLQI)

[redacted]

- SCALPDEX

All questionnaires will be completed in the language the respondent is most familiar with, at the scheduled visit before the subject sees the investigator for clinical assessments. The subject should be given sufficient space and time to complete the questionnaires. **Oral Lichen Planus Symptom Severity Measure (OLPSSM):**

The Oral Lichen Planus Symptom Severity Measure (OLPSSM) was developed by Burke et al. as a PRO-based assessment of the symptom experience of subjects with oral lichen planus (Burke et al 2019) in clinical studies.

It includes 7 triggers contributing to soreness of oral lichen planus: Brushing teeth, eating food, drinking liquids, smiling, breathing through mouth, talking and touching. These 7 items contribute equally to a total OLP symptom severity score, ranging from 0 to 28, with higher scores indicating worse severity.

The OLPSSM is given to all patients in the MLP cohort who have an **oral** affection of the disease.

Dermatology Life Quality Index:

The DLQI is a 10-item general dermatology disability index designed to assess health-related quality of life (HRQoL) in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral warts (Finlay and Khan 1994). The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 32 different skin conditions and is available in 55 languages. The recall period is the last week, and the instrument requires 1 to 2 minutes for completion. Each item has four response categories ranging from 0 (not at all) to 3 (very much). “Not relevant” is also a valid response and is scored as 0. The DLQI total score is a sum of the 10 questions. Scores range from 0 to 30, with higher scores indicating greater HRQoL impairment. Each subscale of the DLQI may also be analyzed separately.

The DLQI is given to all subjects in the study.

Scalpdex:

Scalpdex is a self-administered, health-related quality of life instrument originally developed for scalp dermatitis. This 23-item survey evaluates the subject across three major domains – symptom, functional, and emotion (Chen 2002). Subjects will be asked to score themselves on how true each of the 23 statements has been for them over the past four weeks. The items are

scored on a scale of 0-100, where 0=never, 25=rarely, 50=sometimes, 75=often and 100=all the time.

The Scalpdex is given to subjects in the LPP cohort only.

Patient Assessment of Itch:

Itch is assessed with the following questions:

- "Overall, how severe was your lichen planus-related itching during the past 24 hours?"
- "How severe was your lichen planus-related itching **at the worst moment** during the past 24 hours?"
- "Overall, how bothered were you by your lichen planus-related itching during the past 24 hours?"

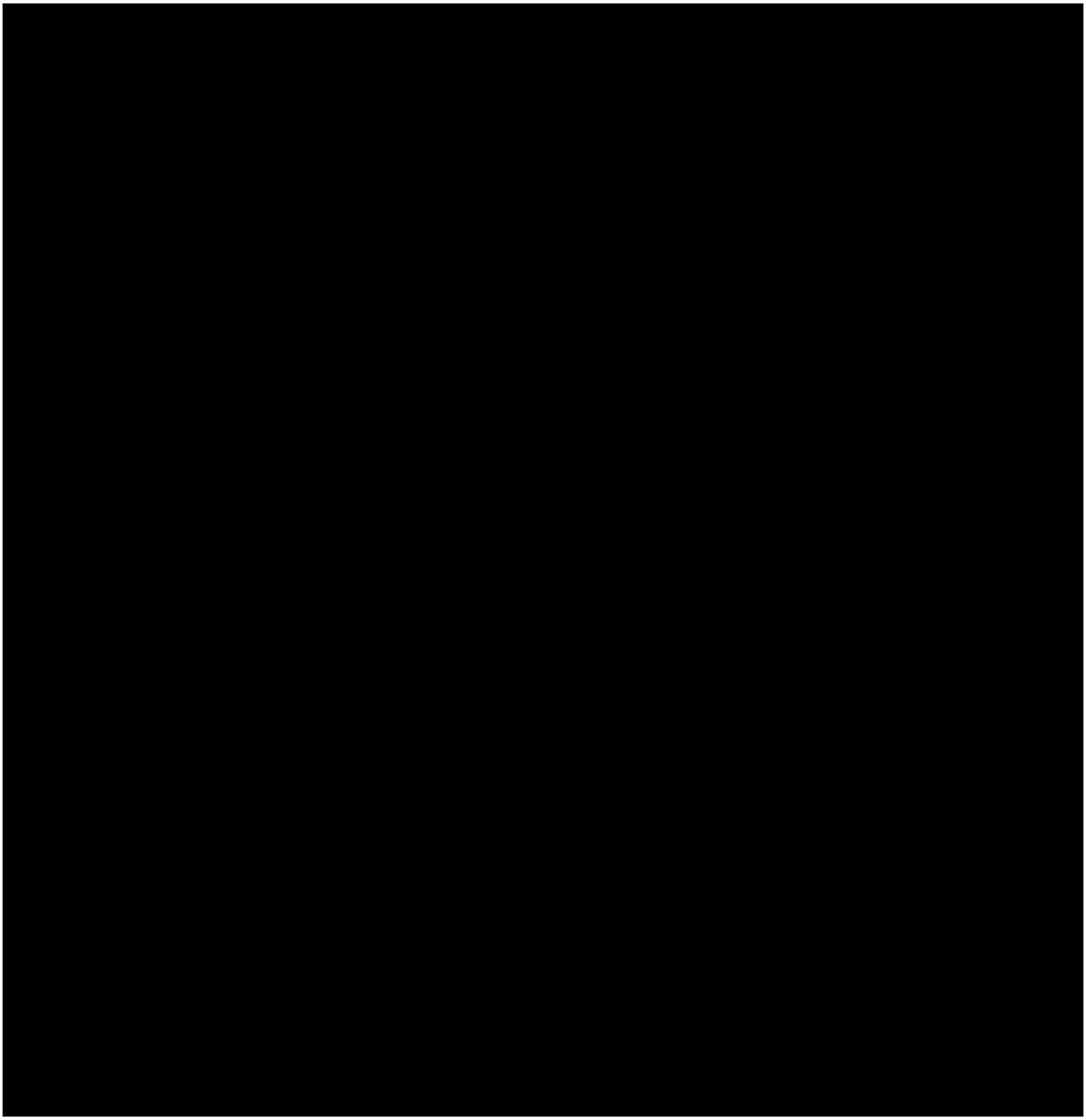
Answers are given on a numeric rating scale (NRS). The Patient Assessment of Itch is done by all subjects.

Patient Assessment of Pain:

Pain is assessed with the following questions:

- "Overall, how severe was your lichen planus-related pain during the past 24 hours?"
- "How severe was your lichen planus-related pain **at the worst moment** during the past 24 hours?"
- "Overall, how bothered were you by your lichen planus-related pain during the past 24 hours?"

Answers are given on a numeric rating scale (NRS). The Patient Assessment of Pain is done by all subjects.



[redacted]

8.5.4 Biomarkers

Tissue biomarkers: Biopsies

Punch biopsies will be taken at the visits defined in the assessment schedule (Table 8-1) and sent to the central laboratory or to a local pathologist. Detailed instructions on the biopsy procedure, sample harvesting, preparation, storage and shipment are provided in the laboratory manual.

The initial biopsies will be taken at the Screening visit, after the urine pregnancy test has shown a negative result for women of childbearing potential. They will be used to obtain a histological confirmation of the diagnosis of lichen planus. The histological confirmation of the diagnosis is mandatory and an inclusion criterion of this study. It is allowed to leave out the biopsy at Screening visit and use a historical biopsy, if available, instead. However, this is only allowed in case the historical biopsy has not been taken longer than 3 months prior to Screening visit and the stained histology slides are available and can be shared with the central laboratory for digitalization. [redacted]

In case the (screening [redacted]) biopsies have been assessed by a local pathologist, stained histology slides should be sent to the central laboratory for digitalization. Appropriate slides representative of the current morphological characteristics and activity of the disease should be selected.

[redacted]

8.5.5 Other Assessments

PRO feedback assessment (optional and only applicable for patients/ sites in the USA)

Using qualitative, semi-structured, open ended questions, feedback from a selected number of trial patients might be asked in optional exit interviews for their experience with the Patient-Reported Outcome measures to inform the future lichen planus clinical trial program.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when the study treatment is stopped earlier than the protocol planned duration (i.e., < Week 32) and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if he/she believes that continuation would negatively impact the subject's well-being. Prior to discontinuation this should be discussed with and communicated to the sponsor's medical expert.

Study treatment must be discontinued under the following circumstances:

- Subject decision
- Withdrawal of consent
- Pregnancy
- A patient on placebo treatment in Treatment Period 1 achieves spontaneous remission (defined by an IGA of 0 or 1) at the Week 16 visit
- Ongoing use of prohibited treatment, use of a prohibited treatment that results in an undue safety risk for the subject as per the investigator’s clinical judgment, or receipt of a live virus vaccine during the study (as detailed in Section 6.2.2)
- Any protocol deviation in which study participation might result in a safety risk to the subject
- Emergency unblinding
- AEs that in the judgment of the investigator/qualified site staff, taking into account the patient’s overall status prevent the subject from continuing study treatment
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient’s overall status, prevents the subject from continuing participation in the study

If discontinuation of study treatment is due to the subject, the investigator should make a reasonable effort to understand the primary reason for the subject’s premature discontinuation of study treatment and to record this information.

Subjects who discontinue study treatment should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.3 'Withdrawal of Informed Consent').

Subjects should continue attending planned site visits and perform the study assessments until the last visit of the study period during which they discontinue (Week 16 or Week 32).

- Subjects, whether they are willing to continue attending further study visits or not, should attend an End of Treatment (EOT) visit of the study period during which they discontinued (EOT 1 for discontinuation during Treatment Period 1 and EOT 2 for discontinuation during Treatment Period 2). The scheduled visit that was planned to take place will then not be performed and will be replaced by the EOT visit.
- Subjects who are willing to continue will attend visits until Week 16 or Week 32 according to the schedule and will then move to the Follow-up period.
- Subjects who are unwilling to continue attending study visits will move directly to the Follow up period after their EOT visit
- Subjects who discontinue study at the same time as study treatment will end their participation after their EOT visit (see also Section 9.1.2).

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to section 6.6.3.

If the subject fails to return for EOT assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the Lost to Follow-up section. This contact should preferably be done according to the study visit schedule.

9.1.2 Discontinuation of study

If a subject discontinues study during a treatment period, EOT visit should be performed (see Section 9.1.1 above). If a subject discontinues study during Follow up period, visit Week 40 should be performed.

If the subject cannot or is unwilling to attend any visit(s) after EOT, the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

Documentation of attempts to contact the subject should be recorded in the source documentation.

9.1.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore
- Does not allow further collection of personal data
- Does not want any further study related contacts
- Does not allow analysis of already obtained biologic material

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For US: all biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: all biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study has occurred.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (and be provided instruction on when the subject should stop self administrating the drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit (Week 40), and any repeat assessments associated with this visit have been documented and

followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

A subject will be considered to have completed the study if he/she received a maximum of 30 weeks of study treatment and upon completion of the scheduled study assessments and procedures up to and including visit Week 40.

The investigator must provide follow-up medical care for all subjects from the study, or must refer them for appropriate ongoing care.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective of whether a clinical event has occurred.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade.

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

2. Its relationship to the study treatment (suspected: Yes/No). If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication), the assessment of causality will usually be ‘Not suspected’. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression

of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject.

3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.

4. Whether it constitutes a serious adverse event (SAE - see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.

5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- dose not changed
- dose reduced/increased
- drug interrupted/withdrawn

6. Concomitant medication or non-drug therapy given

7. Its outcome: not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, fatal, unknown

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 10 weeks following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. Continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Worsening of lichen planus in this study is evaluated via the use of efficacy assessments (e.g. IGA, REU, LPPAI, PSAD) and is **not** expected to be captured as an AE in the CRF capturing adverse events. Exceptions include cases when a new type of lichen planus is diagnosed, or the worsening is so severe that a qualitatively different status is reached.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values, which are considered non-typical in subjects with the

underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 15.1.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days [after the last study visit (Week 40) must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

1. **Screen Failures** (e.g. a subject who is screened but is not treated or randomized): SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.
2. **Randomized OR Treated Subjects**: SAEs collected between time subject signs ICF until 10 weeks after the subject has discontinued or stopped study treatment

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 10-week period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

If a female subject becomes pregnant, the study treatment must be stopped, and the subject asked to read and sign the pregnancy ICF to allow the study doctor to ask about the pregnancy. To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis/ within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same

form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

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

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

Not applicable

10.3 Steering Committee

A steering committee will be established including disease area experts and investigators participating in the trial.

The steering committee will ensure transparent management of the study according to the protocol by recommending and approving modifications as circumstances require. The steering committee will review protocol amendments as appropriate. Together with the clinical trial team, the steering committee will also develop recommendations for publication of study results. The details of the role of the steering committee will be defined in the Steering Committee Charter.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic CRFs (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Subjects will fill in their PRO data in a site based tablet. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study treatment(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by Novartis, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Randomized Analysis Set (RAS) consists of all randomized subjects. Subjects will be analyzed according to the treatment assigned at randomization.

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned. Subjects will be analyzed according to the treatment assigned to at randomization. Mis-randomized subjects (mis-randomized in IRT) will be excluded from FAS. Mis-randomized subjects are defined as cases where IRT contacts were made by the site either prematurely or

inappropriately prior to confirmation of the subject's final randomization eligibility and no study medication was administered to the subject.

The Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

12.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens and any other relevant information will be listed by treatment group and subject.

12.3 Treatments

Data for study drug administration and concomitant therapies will be listed by treatment group and subject.

12.4 Analysis of the primary endpoint(s)

The primary aim of the study is to demonstrate the efficacy of secukinumab (300 mg Q4W) with respect to IGA responder status after 16 weeks of treatment compared to placebo. The detailed definition and the justification of the corresponding primary estimand will be provided in the Estimand Charter.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is the proportion of IGA responder at Week 16, where IGA response is defined as achievement of absolute IGA score ≤ 2.

The analysis of the primary endpoint will be based on the FAS.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary endpoint of IGA response at Week 16 is a binary (yes/no) outcome. Bayesian inference based on the non-informative prior of Beta (1/3, 1/3) for each treatment group will be used to obtain the posterior distrubution of the treatment difference between secukinumab and placebo for the three subtypes, respectively.

The Bayes PoC criteria to be assessed for the primary endpoint are:

1) the probability of the treatment difference greater than zero ($\delta>0$) is greater than 90%;

$Pr(\delta(\text{secukinumab, placebo}),wk16 > 0 \mid \text{data}) > 90\%$

And

2) the probability of the treatment difference exceeding half of the target effect of 0.15 ($\delta>0.15$) is greater than 50%

$Pr(\delta(\text{secukinumab, placebo}),wk16 > 0.15 \mid \text{data}) > 50\%$

where δ denotes the treatment difference between secukinumab and placebo with respect to the IGA response at Week 16

Posterior estimates of the treatment difference and 95% credible interval will be presented. The posterior probabilities of achieving the efficacy criteria will be provided.

12.4.3 Handling of missing values/censoring/discontinuations

Subjects who discontinue treatment before Week 16 will be considered to be failures.

12.4.4 Sensitivity and Supportive analyses

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary endpoints of this study are planned as follow:

Investigator's Global Assessment (IGA) score

IGA responder rate at time points in treatment period 1 other than week 16. The Fisher exact test (if suitable) or the chi-square test will be applied to the IGA responder rate at time points

other than week 16 and estimates of the difference of the IGA responder rate between the 300 mg Q4W treatment regimen and placebo groups together with 95% confidence intervals will be presented.

Proportion (%) of IGA responders will be presented by visit from baseline up to the end of study for each treatment group.

Proportion (%) of subjects achieving 2 points improvement in IGA score will be presented by visit from baseline up to the end of study for each treatment group.

Proportion (%) of IGA 0 or 1 will be presented by visit from baseline up to the end of study for each treatment group.

Dermatology Life Quality Index

Seven scores will be derived from the DLQI: the total score of each of the six dimensions as well as the total score over all items. The higher the score, the more quality of life is impaired. The DLQI total score will be calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0.

- DLQI responder: DLQI total score 0 or 1 will be considered as responder. Proportion (%) of DLQI responder will be presented by visit up to the end of study for each treatment group.
- Summary statistics will be provided for absolute and percentage change from baseline of the total score of each of the six dimensions as well as the total score by visit up to the end of study for each treatment group.

Physician Assessment of Surface Area of Disease (PSAD) for Skin Disease

The number and percentage of subjects in each category will be presented by visit up to the end of study for each treatment group.

Patient Assessment of Itch (NRS)

Summary statistics will be provided for absolute and percentage change from baseline of itching NRS score by visit for each treatment group up to end of study.

Patient Assessment of Pain (NRS)

Summary statistics will be provided for absolute and percentage change from baseline of pain NRS score by visit for each treatment group up to end of study.

Reticular erythematous Ulcerative (REU) score

Summary statistics will be provided for absolute and percentage change from baseline of REU score by visit and for each treatment group up to end of study.

LPP Activity Index (LPPAI)

Subjects with an LPPAI reduction greater than 85% over pretreatment values were considered responders, with 25% to 85% reduction were considered partial responders, and with less than 25% reduction were considered non-responders.

- LPPAI responder and partial responder: LPPAI responder and partial responder will be presented by visit up to the end of study for each treatment group.

- Summary statistics will be provided for absolute and percentage change from baseline of LPPAI score by visit up to the end of study for each treatment group.

Oral Lichen Planus Symptom Severity Measure (OLPSSM):

Summary statistics will be provided for absolute and percentage change from baseline of OLPSSM score by visit for each treatment group up to end of study.

Scalpdex:

Summary statistics will be provided for absolute and percentage change from baseline of Scalpdex score by visit for each treatment group up to end of study.

12.5.2 Safety endpoints

All safety evaluations will be performed on the Safety set.

Adverse events

Treatment emergent AEs (events started after the first dose of study treatment and within 84 days after week 32, or events present prior to the first dose of study treatment but increased in severity based on preferred term within 84 days after week 32) will be summarized. Only primary paths within MedDRA will be considered for AE reporting.

AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a subject reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a subject reported more than one AE within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

Separate summaries will be provided for death, SAE, other significant AEs leading to discontinuation and AEs leading to study treatment discontinuation.

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values.

Clinical laboratory evaluations

The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values.

[redacted]

12.5.6 [redacted]PD relationships

The [redacted] other clinically important endpoints, such as PSAD, REU, LPPAI will be investigated if appropriate.

12.5.7 Patient reported outcomes

Please refer to Section 12.5 or Section 12.6 for the analysis method of Patient reported outcomes.

[redacted]

[redacted]

12.7 Interim analyses

Primary analysis will be performed after all subjects have completed Week 16 visit.

Additional analyses may be performed to support health authority interactions as necessary.

At the end of study, a final analysis of all data collected up to last study visit will be performed when all subjects have completed the last study visit.

12.8 Sample size calculation

Total sample size for this study is 108 with 36 subjects in each subtype

Primary endpoint(s)

For each subtype, 24 secukinumab 300 mg Q4w treatment regimen subjects and 12 placebo subjects assures the 71% probability to claim positive PoC results, based on the assumptions that the placebo IGA responder rate is 20% and secukinumab 300 mg Q4w placebo difference (delta) of the IGA responder rates is at least 30%.

For different response rate assumptions on secukinumab 300 mg Q4w and placebo dose regimens, the below figure and table show that there is not much difference on the probability to claim a successful PoC results between randomization ratios 1:1 and 2:1. Considering the absence of previous lichen planus secukinumab data, randomization 2:1 is chosen for this study to assure more efficacy and safety data on lichen planus secukinumab subjects. The below figure and table also shows the probability to claim a positive PoC results is around 70% when the secukinumab 300 mg Q4w placebo difference (delta) of the IGA responder rates is 30% in any scenario and greater than 85% when the secukinumab 300 mg Q4w placebo difference (delta) of the IGA responder rates is 40% in any scenario.

Figure 12-1 Operating Characteristics on different randomization ratio and different response rate assumption

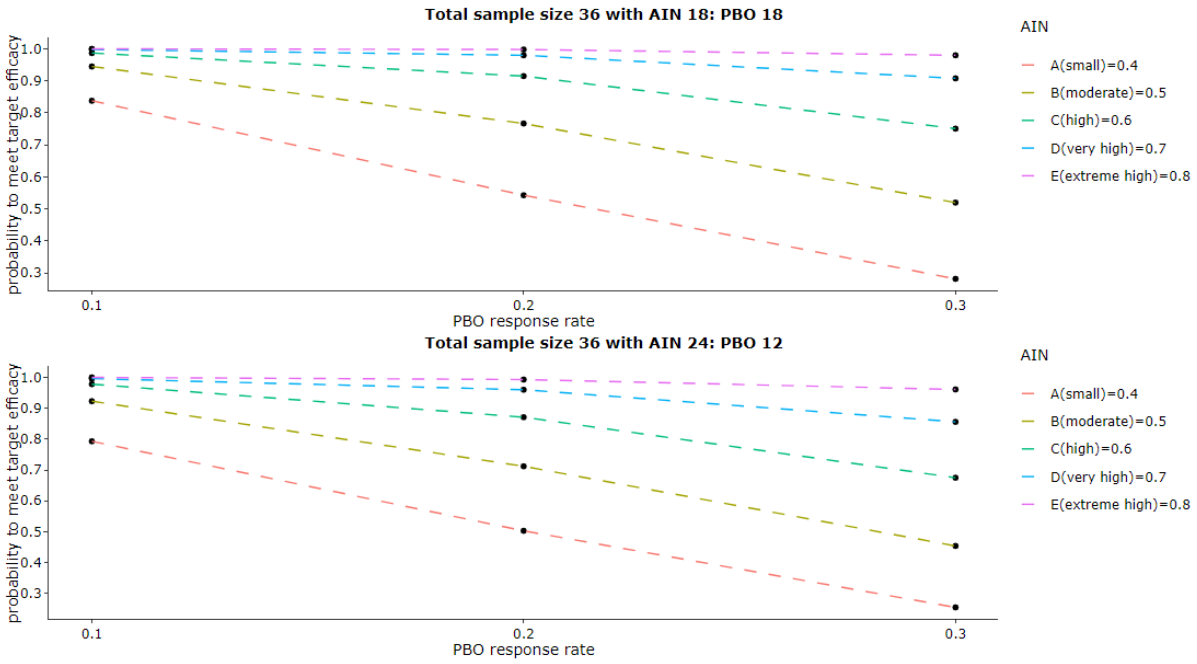


Table 12-1 Operating Characteristics on different randomization ratio and different response rate assumption

Secukinumab response rate	Placebo response rate	Probability to meet target efficacy with AIN 18: PBO 18	Probability to meet target efficacy with AIN 24: PBO 12
A(small)=0.4	0.1	0.838	0.793
B(moderate)=0.5	0.1	0.945	0.923
C(high)=0.6	0.1	0.987	0.978
D(very high)=0.7	0.1	0.998	0.996
E(extreme high)=0.8	0.1	1.000	1.000
A(small)=0.4	0.2	0.543	0.503
B(moderate)=0.5	0.2	0.767	0.712
C(high)=0.6	0.2	0.915	0.871
D(very high)=0.7	0.2	0.980	0.960
E(extreme high)=0.8	0.2	0.998	0.993
A(small)=0.4	0.3	0.282	0.255
B(moderate)=0.5	0.3	0.520	0.454
C(high)=0.6	0.3	0.751	0.675
D(very high)=0.7	0.3	0.908	0.856
E(extreme high)=0.8	0.3	0.980	0.961

Operating Characteristics results are from QTD version 3.0.0

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as *clinicaltrials.gov* and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. *Clinicaltrials.gov*, EudraCT etc) .

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes

13.5 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

13.6 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

14 References

References are available upon request

Balci DD, Inandi T (2008) Dermatology life quality index scores in Lichen Planus: Comparison of psoriasis and healthy controls. Turkderm; 42:127-30.

Bruin G, Loesche C, Nyirady J, et al (2017) Population Pharmacokinetic Modeling of Secukinumab in Patients With Moderate to Severe Psoriasis. J Clin Pharmacol; 57(7):876-85.

Burke LB, Brennan MT, Ni Riordain R, et al (2019) Novel Oral Lichen Planus Symptom Severity Measure for assessing patients' daily symptom experience. Oral Dis; 25(6):1564-72.

Cassol-Spanemberg J, Blanco-Carrion A, Rodriguez-de Rivera-Campillo ME, et al (2019) Cutaneous, genital and oral lichen planus: A descriptive study of 274 patients. Med Oral Patol Oral Cir Bucal; 24(1):e1-7.

Chao TJ (2009) Adalimumab in the management of cutaneous and oral lichen planus. Cutis; 84:325-28.

Chen SC (2002) Scalpdex: A quality-of-life instrument for scalp dermatitis. Arch Dermatol; 138:803-07.

Cheng H, Oakley A, Conaglen JV, et al (2017) Quality of Life and Sexual Distress in Women With Erosive Vulvovaginal Lichen Planus. J Low Genit Tract Dis; 21(2):145–49.

Chiang C, Sah D, Cho BK, et al (2010) Hydroxychloroquine and lichen planopilaris: efficacy and introduction of Lichen Planopilaris Activity Index scoring system. J Am Acad Dermatol; 62:387-92.

Chobanian AV, Bakris GL, Black HR, et al (2003) Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension; 42:1206–52.

Deen K, McMeniman E (2015) Mycophenolate mofetil in erosive genital lichen planus: A case and review of the literature. J Dermatol; 42: 311-14.

Doherty SD, Van Voorhees A, Lebwohl MG, et al (2008) National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. J Am Acad Dermatol; 59:209-17.

Finlay AY, Khan GK. 1994. Dermatology Life Quality Index (DLQI)- a simple practical measure for routine clinical use. Clin. Exp. Dermatol; 19(3):210-16.

Fonda-Pascual P, Fernández-González P, Moreno-Arrones OM, et al (2018) Pustular Secondary Cutaneous Aspergillosis in an Immunosuppressed Patient. Actas Dermosifiliogr; 109:287-90.

Gobbo M, Rupel K, Zoi V, et al (2017) Scoring systems for Oral Lichen Planus used by differently experienced raters. Med Oral Patol Oral Cir Bucal; 22(5):e562-71.

Gorouhi F, Davari P, Fazel N (2014) Cutaneous and mucosal lichen planus: A comprehensive review of clinical subtypes, risk factors, diagnosis, and prognosis. Scientific World Journal; 2014(742826):1-22.

Gueiros LA, Arao T, Souza T, et al (2018) IL17A polymorphism and elevated IL17A serum levels are associated with oral lichen planus. Oral Dis; 24:377–83.

Hazra SC, Choudhury AM, Khondker L, et al (2013) Comparative efficacy of methotrexate and mini pulse betamethasone in the treatment of lichen planus. Mymensingh Med J; 22(4):787-97.

Husein-ElAhmed H, Gieler U, Steinhoff M (2019) Lichen planus: a comprehensive evidence-based analysis of medical treatment. J Eur Acad Dermatol Venereol; 33:1847–62.

[redacted]

Langley RG, Elewski BE, Lebwohl M, et al (2014) Secukinumab in plaque psoriasis- Results of two phase 3 trials. N. Engl. J. Med; 371(4):326-38.

Le Cleach L, Chosidow O (2012) Clinical practice. Lichen planus. N. Engl. J. Med; 366(8):723-32.

Lunge S, Patil S, Manjunathswamy BS (2016) A comparative study of methotrexate & low molecular weight heparin for the treatment of generalized lichen planus. Ind J Clin and Exp Dermatol; 2(4):153-58.

Mancia G (2007) Blood pressure reduction and cardiovascular outcomes: Past, present, and future. Am. J. Cardiol; 100suppl:3J–9J.

Manuel O, Kumar D (2008) QuantiFERON-TB® Gold assay for the diagnosis of latent tuberculosis infection. Expert Rev. Mol. Diagn; 8(3):247-55.

Naeini FF, Saber M, Asilian A, et al (2017) Clinical Efficacy and Safety of Methotrexate versus Hydroxychloroquine in Preventing Lichen Planopilaris Progress: A Randomized Clinical Trial. Int J Prev Med; 8:37-44.

Neuenschwander B, Wandel S, Roychoudhury S, et al (2015) Robust exchangeability designs for early phase clinical trials with multiple strata. Pharmaceut Statist; 15:123-34.

Park HK, Hurwitz S, Woo SB (2012) Oral lichen planus: REU scoring system correlates with pain. Oral Surg Oral Med Oral Pathol Oral Radiol; 114(1):75-82.

Patrick DL, Burke LB, Powers JH, et al (2007) Patient-reported outcomes to support medical product labeling claims: FDA perspective. International Society for Pharmacoeconomics and Outcomes Research; 10(2):S125–S137.

Piboonniyom SO, Treister N, Pitiphat W, et al (2005) Scoring system for monitoring oral lichenoid lesions: a preliminary study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod; 99(6):696-703.

Radwan-Oczko M, Zwyrtek E, Owczarek JE, et al (2018) Psychopathological profile and quality of life of patients with oral lichen planus. J Appl Oral Sci; 26:1-9.

Schmidt T, Solimani F, Pollmann R, et al (2018) TH1/TH17 cell recognition of desmoglein 3 and bullous pemphigoid antigen 180 in patients with lichen planus. J. Allergy Clin. Immunol; 142(2):669-72.

Shaker O, Hassan AS (2012) Possible role of interleukin-17 in the pathogenesis of lichen planus. Br. J. Dermatol; 166:1367-68.

Solimani F, Pollmann R, Schmidt T, et al (2019) Therapeutic Targeting of Th17/Tc17 Cells Leads to Clinical Improvement of Lichen Planus. Front Immunol; 10:1-10.

Thandar Y, Maharajh R, Haffejee F, et al (2019) Treatment of cutaneous lichen planus (Part 1): A review of topical therapies and phototherapy. Cogent Medicine; 6:1-21.

Thongprasom K, Dhanuthai K (2008) Steriods in the treatment of lichen planus: a review. J Oral Sci; 50(4):377-85.

Tziotzios C, Brier T, Lee JYW, et al (2018) Lichen planus and lichenoid dermatoses: Conventional and emerging therapeutic strategies. J. Am. Acad. Dermatol; 79:807-18.

Welz-Kubiak K, Reich A, Szepietowski JC (2017) Clinical Aspects of Itch in Lichen Planus. Acta Derm. Venereol; 97:505–08.

Yang CC, Khanna T, Sallee B, et al (2018) Tofacitinib for the treatment of lichen planopilaris: A case series. Dermatol Ther; 31:1-4.

Zakrzewska JM, Chan ES, Thornhill MH (2005) A systematic review of placebo-controlled randomized clinical trials of treatments used in oral lichen planus. Br. J. Dermatol; 153(2):336-41.

Zhang J, Zhou G, Du GF, et al (2011) Biologics, an alternative therapeutic approach for oral lichen planus. J. Oral Pathol. Med; 40:521–24.

15 Appendices

15.1 Appendix 1: Clinically notable laboratory values and vital signs

Clinically notable laboratory values

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests.

No specific action is pre-defined within this protocol to respond to specific abnormal laboratory values, as it will be decided by the investigator whether and which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the subject.

Liver Function and Related Variables

Alanine transaminase (ALT) (SGPT): > 3 x Upper Limit of Normal (ULN)

Aspartate transaminase (AST) (SGOT): > 3 x ULN

Total bilirubin: > 2 x ULN

Alkaline phosphatase: > 2.5 x ULN

Renal Function

Creatinine (serum): > 1.5 x ULN

Hematology

Hemoglobin: ≥ 2 g/dl decrease from baseline

Platelet count: < Lower Limit of Normal (LLN)

White blood cell count: < 0.8 x LLN

Neutrophils: < 0.9 x LLN

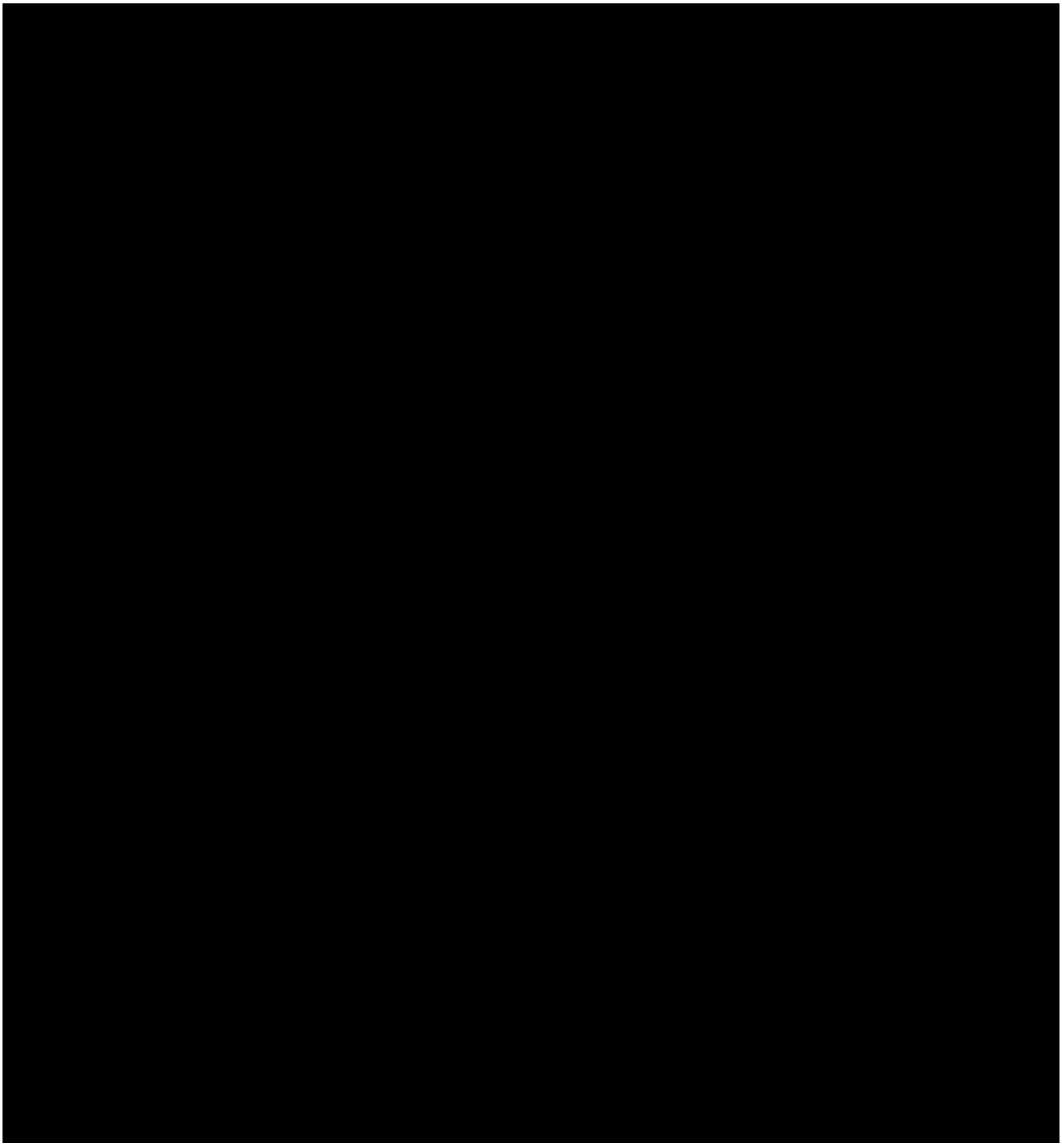
Eosinophils: > 1.1 x ULN

Lymphocytes: > 1.1 x ULN

Clinically notable vital signs

Notable values for Vital signs are defined in Table 8-4.

No specific action is pre-defined within this protocol to respond to specific abnormal vital signs, as it will be decided by the investigator whether and which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the subject.



15.3 Appendix 2: Determination of Tuberculosis status

Determination of tuberculosis (TB) status will be required before administration of study treatment and should be performed as defined by local guidelines. TB status must be determined by medical history, signs, symptoms and TB central lab testing. Any significant findings will be recorded in the relevant TB assessment eCRF and the Medical History eCRF, as necessary.

A central lab testing will be performed to assess the TB status at screening for all subjects. This test will only be used to determine subject's eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection (Doherty et al 2008).

This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin vaccination or by exposure to other Mycobacteria species. Furthermore, this test, in contrast to the purified protein derivative (PPD) skin test, is also insensitive to a booster effect since the subject is not exposed to the vaccine. The assay measures the production of interferon-gamma and presents it relative to a negative and a positive control sample (Manuel and Kumar 2008). The tuberculosis assay test will be supplied by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the study-specific laboratory manual.

Positive or indeterminate tests must be recorded on the Tuberculosis assessment eCRF; the workflow of sample handling in case of positive or indeterminate test results is provided in Figure 15-1.

a. If the test result is **negative**, the subject may be randomized.

b. If the test result is **positive**, the investigator should perform a work-up for the test result as per local procedures. If a TB work-up was conducted prior to the screening of the subject, results of the work-up can be used to assess eligibility if the work-up was conducted within 12 weeks prior to randomization.

Subjects **positive** for latent TB per work-up may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration. Subjects positive for active TB per work-up are not eligible for the study. Subjects negative for TB (no signs of latent or active TB) per work-up may be randomized to the trial.

c. If the test result is **indeterminate**, the investigator **may repeat the test once or may proceed directly to perform the work-up** for the test result as per local procedures. This action is at the discretion of the investigator. If a TB work-up was conducted prior to the screening of the subject, results of the work-up can be used to assess eligibility if the work-up was conducted within 12 weeks prior to randomization.

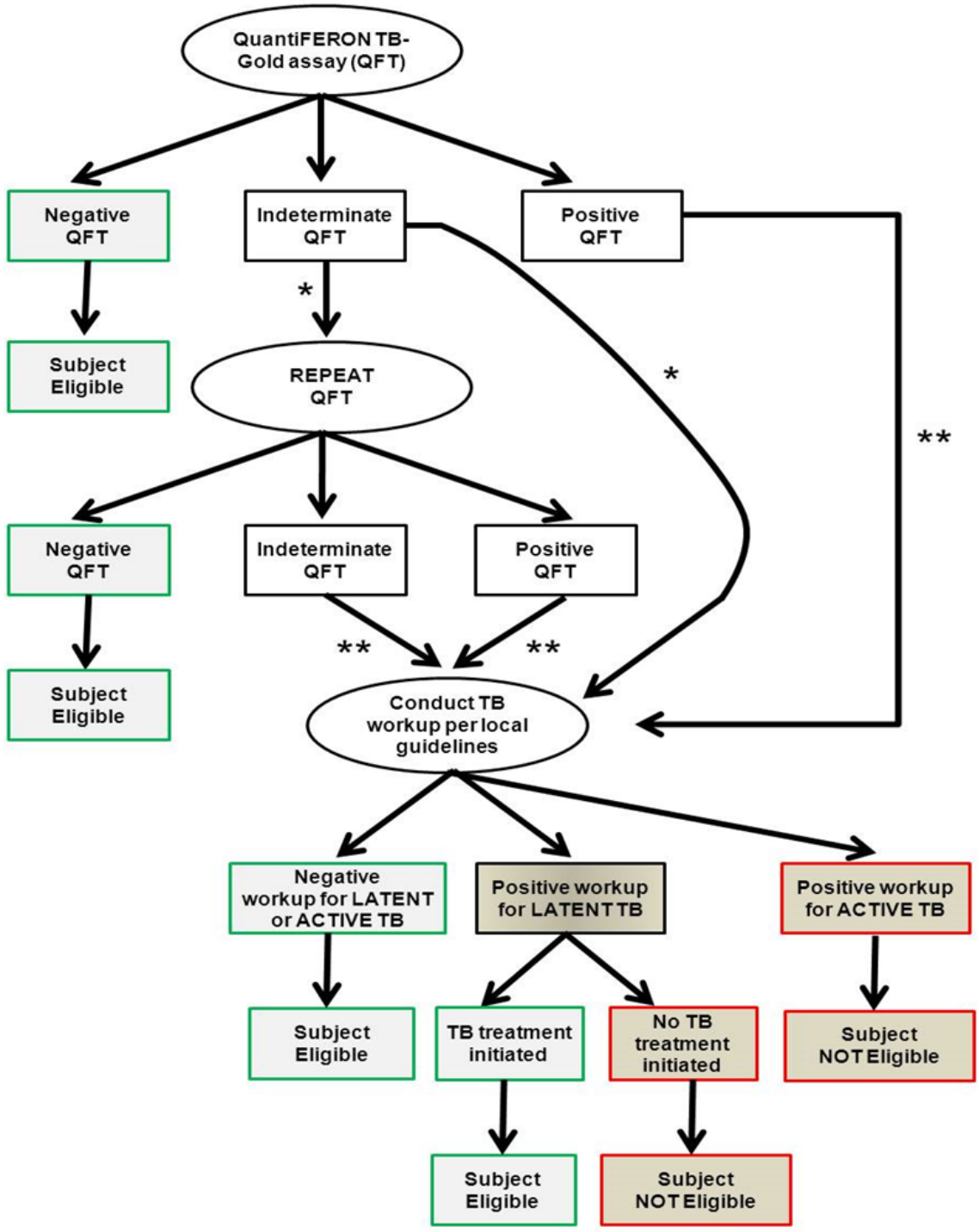
i. If the second test is, the subject may be randomized.

ii. If the second test is positive or indeterminate, the investigator should perform workup as per local guidelines. Subject positive for **latent** TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration. The subject will not be eligible for randomization if "active tuberculosis is present "or" latent tuberculosis is present" and is untreated per local guidelines.

iii. Subjects negative for TB per workup (no signs of latent or active TB) may be randomized to the trial if the workup was conducted 12 within weeks prior to randomization. .

If eligibility is being assessed with only 1 test result and a TB work-up (i.e., no second TB test will be performed), the TB test to assess eligibility must have been done via the central laboratory for the study within the Screening Period (within 4 weeks prior to randomization) and TB work-up will only be considered if it was completed **within 12 weeks** prior to randomization.

Figure 15-1 Tuberculosis screening flowchart



The subject will not be eligible for randomization if "active tuberculosis is present "or if "latent tuberculosis is present and is untreated as per local guidelines."

* If the first QuantiFERON® TB-Gold In-Tube test (QFT) is indeterminate, the investigator may choose to perform a second QFT or refer the subject for tuberculosis workup per local guidelines.

** If the result of any QFT is "positive" or the results of 2 sequential QFTs are "indeterminate", the subject must be referred to have a tuberculosis workup per local guidelines (if no workup within 12 weeks prior to randomization is available).