NOVARTIS

Novartis Research and Development

AIN457

Clinical Trial Protocol CAIN457M2302

A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa (SUNRISE)

Document type:	Amended Protocol Version
EUDRACT number:	2018-002062-39
Version number:	02 (Clean)
Clinical trial phase:	III
Release date:	08-Jan-2021

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

List of tables

[redacted]

List of figures

[redacted]

List of abbreviations

A	abscess
AE	adverse event
ALT	alanine aminotransferase
ALP	Alkaline Phosphatase
AN	abscesses and inflammatory nodules
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BD-2	beta-defensin-2
CDS	core data sheet
CFR	Code of Federal Regulation
COAs	clinical outcome assessments
COVID-19	Corona Virus Disease 2019
CRP (hsCRP)	(high sensitivity) C-reactive protein
CSR	clinical study report
CTC	Common Toxicity Criteria
CTT	clinical trial team
CV	coefficient of variation
DF	Draining fistulae
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
eCRF	electronic case report/record form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	end of treatment
EPAR	European public assessment report
EQ-5D	Euro-QoL (EQ-5D-3L) - standardized tool to assess quality of life in 3 levels
ESR	erythrocyte sedimentation rate
EU	European Union
F	fistulae
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HbA1c	hemoglobin A1c
HDL	high density lipoprotein
HiSCR	Hidradenitis Suppurativa Clinical Response
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HS	hidradenitis suppurativa
HS-PGA	Hidradenitis Suppurativa Physician's Global Assessment
i.v.	intravenous
IB	Investigator’s Brochure
ICF	informed consent form

[redacted]

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IFU	instructions for use
IG	immunogenicity
IgG1	immunoglobulin G1
IL-17A	interleukin-17A
IRB	institutional review board
IRT	interactive response technology
LDL	low density lipoprotein
LLN	lower limit of normal
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mHSS	modified Hidradenitis Suppurativa Score
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	mixed model repeated measures
mRNA	messenger RNA
N	inflammatory nodules
NRS	Numerical Rating Scale
PD	pharmacodynamic(s)
PFS	pre-filled syringe
PGI-c	Patient Global Impression of change
PGI-s	Patient Global Impression of severity
PK	pharmacokinetic(s)
PPD	purified protein derivative
PRO	patient reported outcome
PSUR	Periodic Safety Update Report
PTY	patient-treatment years
q2w	once every two weeks
q4w	once every four weeks
QFT	QuantiFERON® TB-Gold In-Tube assay
QoL	quality of life
RAS	randomized analysis set
RNA	ribonucleic acid
s.c.	subcutaneous
SAE	serious adverse event
SC	steering committee
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TNF-α	tumor necrosis factor-α
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WBC	white blood cell(s)

[redacted]

WHO	World Health Organization
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem
β-hCG	β-human chorionic gonadotropin

[redacted]

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
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
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.
Part	A single component of a study which 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 drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
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.

[redacted]

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.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time-points.
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data.

[redacted]

Amendment 2 (08-Jan-2021)

Amendment Rationale

The purpose of this amendment is to update the statistical analysis section including adjusting the split of the overall alpha level allocating 80% to testing the high dose secukinumab regimen (300 mg q2w) versus placebo, revising the definition of the baseline for assessments and adding additional analyses as described below.

This change has been deemed necessary following the recently available results from study CAIN457A2324, conducted in patients affected by moderate to severe plaque psoriasis and body weight ≥90kg and treated with secukinumab 300 mg every four weeks (q4w) or every two weeks (q2w). The study CAIN457A2324 showed that in psoriasis patients who weigh ≥90kg, secukinumab 300 mg q2w demonstrates a better treatment effect, without altering the well characterized safety profile of secukinumab. Patients with Hidradenitis Suppurativa (HS) are generally heavier than patients with psoriasis (Storer et al 2018), and it seems reasonable to assume that the same weight-based response seen in psoriasis could apply to HS patients as well. These new findings, paired with the absence of safety concerns noted by the HS Data Monitoring Committee (DMC) when evaluating the 300 mg q2w data from the CAIN457M2301 and CAIN457M2302 studies (17-Jun-2020), and the safety profile seen in study CAIN457A2324, support the revision of the statistical analysis section.

In addition, this amendment introduces the value of the individual lesion count assessed at the baseline visit only to be used as 'baseline' in the statistical analyses, instead of the weighted average across the two screening visits and the baseline (randomization) visit. This change follows the guidance from the FDA advice letter on studies CAIN457M2301 and CAIN457M2302 dated 20-Aug-2019 stating: "As the treatment will be initiated at baseline and not at screening visits, for interpretation of study findings, we recommend that you use the assessments collected at the time of the baseline visit" and also guidance from the FDA advice letter on studies CAIN457M2301/M2302 dated 10-Nov-2020 "For interpretation of study findings, we maintain our recommendation that you use the assessments collected at the randomization visit as the baseline value". The weighted average value will still be considered in sensitivity analyses.

In order to take into account the variability and the subjectivity of the Hidradenitis Suppurativa Clinical Response (HiSCR), the inter-rater variability when evaluating the draining fistulae and their longevity often requiring surgical excision (Revuz J 2009), a secondary endpoint evaluating **only** the abscesses and inflammatory nodules (AN) count has been added. Analyzing AN count on the original, continuous scale, enables a more sensitive and granular approach to summarizing the clinical effect of treatment (Kimball et al 2018).

Moreover, based on the evidence that biologic-naive (bio-naive) patients respond better to biologic therapies, including secukinumab, compared to those who are bio-experienced (Garcia-Montoya and Marzo-Ortega 2018), and considering that it is plausible to assume a dose-response influenced by weight, the exploratory objective section has been updated to include a specific analysis to evaluate the benefit of secukinumab in the bio-naive population and in the patients with body weight above and below 90 kg. Furthermore, an exploratory objective related

[redacted]

to C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) has been added to explore treatment effect with regard to inflammatory markers.

Lastly, as introduced in the previous Amendment 01, the number of patients to be randomized has been formally increased to account for the disruptive impact of the COVID-19 pandemic.

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.

The major changes made to the protocol are listed below.

- Section 2 and Table 2-1 have been updated with the addition of the reduction of AN count as secondary and exploratory endpoints, evaluation of inflammatory markers (ESR and CRP) and of the achievement of HiSCR in bio-naive patients, and in patients with body weight lower and higher than 90 kg (<90 kg and ≥90 kg) as exploratory subgroup analyses.
- Section 3, Section 5 and Section 12.8 have been updated with the increase of the target population (approximately 541 patients).
- Section 4.2 Rationale for dose/regimen and duration of treatment and Section 4.5 have been updated including the available data from the recent CAIN457A2324 study.
- Section 12.4.1 has been edited with updated baseline definition.
- Section 12.4.4 has been updated with additional sensitivity analysis for baseline and weighted baseline values
- Section 12.5.1 and Appendix 16.3 have been modified to reflect the updated alpha allocation.
- Section 12.6 has been updated with the pre-specified subgroup analyses.
- Section 12.8, Section 12.8.1 Primary endpoint(s) and Section 12.8.2 have been updated with power calculations.

This protocol amendment also includes corrections of minor errors across sections of the protocol.

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 require IRB/IEC and Health Authority approval according to local regulations prior to implementation. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 1 (17-Jun-2020)

Amendment rationale

The rationale for the amendment reflects the guidance released from several Health Authorities (FDA, EMA, MHRA) to introduce a level of flexibility in drug dispensation, protocol assessments and visit schedule if a major health care event requires it (i.e. COVID-19 pandemic).

While adherence to protocol procedure and GCPs remains mandatory, Novartis has edited the wording in some sections of the protocol to allow the patients in the trial to continue treatment while being monitored for safety in these situations.

These changes will reduce the risk of exposure for patients and site staff, and potentially the risk for transmission of infectious diseases (e.g. COVID-19).

In addition, a 'special scenario' has been added to the study design to ensure a careful assessment of lesion count at Week 52, by allowing for the possibility to perform up to 3 unscheduled visits.

In case of a global health crisis impeding the patients (or the sites) to attend (or perform) Week 52 study visit on site, the patients in the study will be allowed to receive additional study treatment up to 12 weeks after Week 50, or until they can return to the study site to perform the Week 52 assessment (whichever occurs first).

This additional, optional phase will permit the patients to be assessed for eligibility to roll over in the 4 years, long-term extension study. During this period, the patients will continue to be monitored for safety.

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.

The major changes made to the protocol are listed below.

- Section 3, Section 8 and Table 8-1 have been edited with the option of performing up to 3 unscheduled visits if, in case of pandemic/epidemic health crisis, the patient cannot be assessed on site for the Week 52 lesion count.
- Section 3, Section 5, Section 12.4.3 and Section 12.8 have been modified to allow the recruitment of additional patients if missing data due to a global health event jeopardize the power of the predefined statistical tests. The number of patients that may be included to compensate the missing data is not expected to exceed 15% of the pre-planned population.
- Section 3, Section 6.7, Section 6.7.2, Section 8, Section 8.3, Section 8.4 and Section 11.3 have been modified to allow study drug shipment to subjects for home administration, as well as remote contact to collect safety information, remote site initiation visits or monitoring related activities in case of pandemic/epidemic events.
- Section 5.2 and Section 8.2.8 have been edited adding clarity on the process to assess the eligibility of patients with latent TB at screening.
- Section 7 has been edited include the possibility for patients to provide their consent remotely, if appropriate.

[redacted]

- Section 8.3.7 has been edited to clarify the mandatory completion of the HS Patients' Diary in countries where available.

This protocol amendment also includes corrections of minor errors or inconsistencies across sections of the protocol and increase clarity of the text.

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 require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CAIN457M2302
Full Title	A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa
Brief title	Study of efficacy and safety of two secukinumab dose regimens in subjects with moderate to severe hidradenitis suppurativa
Sponsor and Clinical Phase	Novartis/Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to demonstrate superiority of secukinumab at Week 16, based on HiSCR rates versus placebo, along with the maintenance of efficacy of secukinumab at Week 52 in subjects with moderate to severe HS. Moreover, this study will also assess the safety and tolerability of secukinumab.
Primary Objective(s)	The primary objective of this study is to demonstrate the efficacy of secukinumab compared to placebo with respect to HiSCR after 16 weeks of treatment
Secondary Objectives	To demonstrate the efficacy of secukinumab compared to placebo with respect to: ● percentage change in AN count ● proportion of patients with HS flares ● proportion of patients with clinical response in HS related skin pain after 16 weeks of treatment
Study design	This is a multicenter, randomized, double-blind, placebo controlled, parallel group study with two secukinumab dose regimens in approximately 541 patients with moderate to severe HS. The study consists of: Screening (up to 4 weeks), Treatment Period 1 (16 weeks) and Treatment Period 2 (36 weeks). Subjects who prematurely discontinue the study, or who complete the study and cannot or do not wish to continue in a planned optional extension study, will enter a post-treatment Follow-Up period (8 weeks).
Population	The study population will consist of a representative group of adult male and female subjects (≥ 18 years) with moderate to severe HS. It is aimed to randomize approximately 541 subjects in approximately 132 study sites worldwide. Up to 40% of the subjects will be allowed to enter the study on treatment with stable dose of antibiotics.
Key Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. 2. Male and female patients ≥ 18 years of age. 3. Diagnosis of HS ≥ 1 year prior to baseline. 4. Patients with moderate to severe HS defined as: ● A total of at least 5 inflammatory lesions, i.e. abscesses and/or inflammatory nodules AND ● Inflammatory lesions should affect at least 2 distinct anatomic areas 5. Patients agree to daily use of topical over-the-counter antiseptics on the areas affected by HS lesions while on study treatment.

[redacted]

Key Exclusion criteria	1. Total fistulae count ≥ 20 at baseline. 2. Any other active skin disease or condition that may interfere with assessment of HS. 3- Active ongoing inflammatory diseases other than HS that require treatment with prohibited medications (see Table 6-2). 4. Use or planned use of prohibited treatment. Washout periods detailed in the protocol have to be adhered to (see Table 6-2). 5. History of hypersensitivity to any of the study drug constituents. 6. 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 keratoses 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). 7. Pregnant or lactating women.
Study treatment	● Secukinumab 300 mg solution for s.c. injection in a 2 ml PFS ● Placebo solution for s.c. injection in a 2 ml PFS
Efficacy assessments	Efficacy assessments related to the primary and secondary objectives include: ● Individual lesion count used for calculation of Hidradenitis Suppurativa Clinical Response (HiSCR) and HS flare ● Patient's Global Assessment of Skin Pain - NRS in the past 24 hours
Key safety assessments	● Evaluation of all AEs and SAEs ● Physical examination ● Vital signs ● Laboratory evaluations (e.g. hematology, clinical chemistry, urinalysis) ● Immunogenicity (assessment of anti-AIN457 antibody development) ● Pregnancy

Other assessments	● Additional efficacy assessments linked to the exploratory objectives include:
	  ● Modified Hidradenitis Suppurativa Score (mHSS);
	  ● HS-Physician's Global Assessment (HS-PGA);
	  ● Dermatology Life Quality Index (DLQI);
	  ● Health Status Questionnaire (EQ-5D-3L);
	  ● Patient Global Impression of severity (PGI-s);
	  ● Patient Global Impression of change (PGI-c);
	  ● Work Productivity and Activity Impairment - Specific Health Problem (WPAI-SHP);
	  ● HS Symptom Diary
	● Exploratory biomarkers
	● Pharmacokinetic parameter

Data analysis	The primary endpoint of the study is HiSCR at Week 16, defined as at least a 50% decrease in the Abscess and inflammatory Nodule (AN) count compared to baseline with no increase in the number of abscesses and/or in the number of draining fistulae from baseline to Week 16. The secondary endpoints of this study are as follows: ● Percentage change from baseline in AN count at Week 16 ● Flare over 16 weeks: Patients who experience at least one flare over 16 weeks. Flare is defined as at least a 25% increase in AN count with a minimum increase of 2 AN relative to baseline. ● Pain/NRS30 at Week 16: Patients achieving NRS30 at Week 16, among patients with baseline NRS ≥ 3. NRS30 is defined as at least a 30% reduction and at least 2 unit reduction from baseline in the Patient's Global Assessment of Skin Pain. The statistical hypothesis for the primary endpoint being tested is that there is no difference in the proportion of HiSCR at Week 16 in any of the secukinumab regimens versus placebo regimen. H1: secukinumab 300 mg q2w s.c. is not different to placebo regimen with respect to HiSCR after 16 weeks of treatment. H2: secukinumab 300 mg q4w s.c. is not different to placebo regimen with respect to

[redacted]

	HiSCR after 16 weeks of treatment. The primary analysis method will be logistic regression with treatment group, geographical region, Hurley stage, use of antibiotic, baseline body weight and baseline AN count as explanatory variables. Odds ratios will be computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted. In case of response rates of 0% or of 100% in one of the treatment groups, Fisher's exact test will be applied. Risk difference and confidence intervals for risk difference will be provided. The statistical hypotheses for the secondary endpoint being tested are that: ● there is no difference in mean of percentage change from baseline in AN count in any of the secukinumab regimens versus placebo regimen. ● there is no difference in the proportion of flare over 16 weeks in any of the secukinumab regimens versus placebo regimen ● there is no difference in the proportion of NRS30 at Week 16 in any of the secukinumab regimens versus placebo regimen H3: secukinumab 300 mg q2w s.c. is not different to placebo regimen with respect to the percentage change from baseline in AN count at Week 16 H4: secukinumab 300 mg q4w s.c. is not different to placebo regimen with respect to the percentage change from baseline in AN count at Week 16 H5: secukinumab 300 mg q2w s.c is not different to placebo regimen with respect to flare over 16 weeks of treatment H6: secukinumab 300 mg q4w s.c. is not different to placebo regimen with respect to flare over 16 weeks of treatment H7: secukinumab 300 mg q2w s.c. is not different to placebo regimen with respect to NRS30 at Week 16 H8: secukinumab 300 mg q4w s.c. is not different to placebo regimen with respect to NRS30 at Week 16 For the secondary endpoint of percentage change in AN count from baseline to Week 16, an analysis of covariance (ANCOVA) model will be fitted to estimate the treatment differences between the two secukinumab regimens and placebo with treatment group, baseline AN count, Hurley stage, use of antibiotic, geographical region and baseline body weight as covariates. The analysis method for flare up to Week 16 and Pain/NRS30 at Week 16endpoints will be the logistic regression: with treatment group, Hurley stage, geographical region, use of antibiotic, baseline body weight and baseline AN counts as explanatory variables for flare endpoints; and with treatment group, Hurley stage, region, use of antibiotic, baseline body weight and baseline NRS as explanatory variables for pain endpoints. Odds ratios will be computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted. In case of response rates of 0% or of 100% in one of the treatment groups, Fisher's exact test will be applied. Risk difference and confidence intervals for risk difference will be provided.
Key words	hidradenitis suppurativa, HS, IL-17A, monoclonal antibody, AIN457, secukinumab, HiSCR, pain, efficacy, safety

[redacted]

1 Introduction

1.1 Background

Hidradenitis suppurativa (HS), also called "acne inversa" or "maladie de Verneuil", is a chronic, recurrent, and debilitating inflammatory skin condition that typically presents with deep, inflammatory, painful lesions in apocrine gland-bearing parts of the body. The most common areas affected are the axillae, the groin, and the anogenital region (Fimmel and Zouboulis 2010, Jemec 2012).

HS is currently considered an inflammatory disease of the pilosebaceous follicle with an underlying immune system imbalance that occurs in genetically predisposed individuals (Kelly et al 2014).

The disease starts after puberty and women are more frequently affected than men (3:1). Risk factors include obesity and smoking. Although epidemiological prevalence estimates vary widely (0.03 to 4.3%), and geographical differences exist, a prevalence of approximately 0.1 to 1% is accepted by the scientific community (Deckers et al 2014, Garg et al 2017).

The clinical manifestations of HS are heterogeneous, but the disease tends to manifest with chronic, relapsing, deep, painful, inflammatory skin lesions, mostly inflammatory nodules and abscesses, leading to possible drainage and suppuration. Inflammatory lesions are complicated during disease progression by sinus tract formation and fistulization, and may lead to hypertrophic scarring with a possible impact on functional use.

HS is associated with pain, malodorous discharge from the wounds, and scarring, and it frequently has devastating psychosocial effects. HS is a profoundly debilitating disease with a high negative impact on quality of life (QoL), with multiple studies confirming that the impact is greater than that seen with other dermatologic diseases (Deckers and Kimball 2016). Patients with HS also often suffer from depression, social isolation, have an impaired sexual health, and may have difficulty performing their work duties (Deckers et al 2014, Janse et al 2017).

HS is difficult to treat. Official European treatment guidelines have only been developed in 2015 and suggest that patients should be provided with adjuvant, medical and surgical therapy (Zouboulis et al 2015).

While topical antibiotics can be used for mild cases, long courses of multiple antimicrobial therapy are preferred for moderate to severe HS, generally with tetracyclines or a combination of clindamycin and rifampicin, which can be followed by maintenance with chronic antibiotic treatment for months or even years (Zouboulis et al 2015, Bettoli et al 2016, Dessinioti et al 2016).

However, it is widely recognized that HS is a chronic inflammatory condition, not an infectious disease (Jemec 2012). Therefore, anti-inflammatory agents are an alternative and probably more appropriate approach than antibiotics.

Over time, the consequence of chronic, recurrent, inadequately treated inflammation is irreversible fibrosis, which does not respond to medical therapy. Once lasting anatomical changes occur, the only therapeutic option to reduce the volume of fibrotic tissue and improve functionality in the areas of affected skin is surgery (Andersen and Jemec 2017).

[redacted]

In 2015, adalimumab (Humira®), a recombinant human monoclonal immunoglobulin G1 (IgG1) antibody to soluble and membrane bound tumor necrosis factor α (TNF-α), received regulatory approval for the treatment of moderate to severe HS.

Efficacy has been seen with adalimumab, with Hidradenitis Suppurativa clinical response (HiSCR) response rates over placebo of approximately 16% (41.8% adalimumab vs 26% placebo) and 31% (58.9% adalimumab vs 27.6% placebo) as reported in PIONEER I and II studies, respectively (Kimball et al 2016). As captured in the adalimumab labels, adalimumab is associated with an increased safety risk for serious infections including tuberculosis (TB), invasive fungal infections and other opportunistic infections. An increased incidence of malignancies has also been reported with adalimumab.

There is an unmet need for systemic therapies that effectively reduce inflammation while having a favorable safety profile.

Secukinumab (AIN457) is a recombinant high-affinity fully human monoclonal anti-human interleukin-17A (IL-17A) antibody of the immunoglobulin G1 (IgG1)/kappa isotype. Secukinumab is selective for human IL-17A and potently neutralizes the bioactivity of this cytokine. IL-17A is the central cytokine in multiple autoimmune and inflammatory processes.

In HS, there is increasing scientific evidence to support the role of IL-17 in the pathogenesis of the disease:

- Upregulation of mRNA for IL-17A in lesions of patients with HS and psoriasis, while levels in control and atopic dermatitis patients were not increased (Wolk et al 2011)
- High levels of IL-17A or downstream markers are expressed in inflammatory HS lesions (Kelly et al 2015, Lima et al 2016):
  - IL-17 producing cells are present in lesional and peri-lesional HS skin and may contribute to the initiation of inflammatory processes.
  - Massive influx of IL-17-expressing cells (neutrophils and/or T-lymphocytes) has been observed in deep dermal infiltrates.
- Increased IL-17 serum levels have been observed in patients with HS; a tendency toward higher serum concentrations of IL-17 has been reported for patients with more advanced disease (Matusiak et al 2016).

Secukinumab is approved in more than 80 countries worldwide. The product is indicated for the treatment of moderate to severe plaque psoriasis, ankylosing spondylitis, psoriatic arthritis, non-radiographic axial spondyloarthritis, and is being evaluated in other inflammatory conditions such as juvenile idiopathic arthritis and pediatric psoriasis.

As of 25-Jun-2020, over 22,000 patients have received secukinumab in clinical studies at doses ranging from single and/or multiple doses of 0.1 mg/kg to 30 mg/kg intravenous (i.v.) and 25 mg to 300 mg subcutaneous (s.c.) (Investigator's Brochure (IB) Edition 20, data cut-off 25–Jun-2020). The cumulative patient exposure from post-marketing experience for all approved indications since the International Birth Date of the product is approximately 467,835 patient-treatment years (PTY) (Periodic Safety Update Report (PSUR), data cut-off 25-Dec-2019). Full safety results including all reported adverse events (AEs) are currently available for completed studies across different indications. In general, these results show comparable numbers of AEs in subjects treated with secukinumab compared to placebo without indication of any specific

[redacted]

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

In a case report by Thorlacius, substantial improvement was observed in the number of boils and pain severity in one patient with HS treated with secukinumab 300 mg every 4 weeks, after loading doses of 300 mg weekly for 4 weeks (Thorlacius et al 2017). A second case report described a patient treated with secukinumab who experienced significant improvement with secukinumab in a similar dosing regimen (Schuch et al 2018) further supporting that treatment with an anti-IL-17 antibody could be an effective therapy for HS. A third case report (Pandey et al 2018) described a patient with HS who responded to secukinumab treatment for a period of 6 months and was able to discontinue treatment after satisfactory improvement. The patient remained symptom free for three months following discontinuation, and began successful re-treatment with secukinumab after lesions reappeared. No unexpected safety signals were observed in all three patients.

Early clinical evidence of the effects of another Novartis anti-IL-17 antibody, CJM112, supports the potential of an anti-IL-17 antibody as an effective therapy for patients with HS. The results of a randomized, double-blind, placebo-controlled Phase 2 study in 66 patients with moderate to severe HS (study CCJM112X2202) showed a statistically significant increase in the responder rate (HS Physician's Global Assessment (HS-PGA) responder rate 32.3% vs 12.5%, p = 0.028) at Week 16. Numerical decreases in inflammatory lesions were similar to that observed with adalimumab (-2.6 inflammatory lesions in CJM112 relative to placebo vs -2.4 to -3.0 in adalimumab relative to placebo) (Novartis data on file).

Based on the available data, secukinumab has the potential to be an effective therapy for moderate to severe HS with efficacy at least similar to that of adalimumab, a better safety profile and sustained low immunogenicity supporting long-term treatment.

The aim of the present study is to assess the efficacy, safety, pharmacokinetics and tolerability of two dose regimens of secukinumab in patients with moderate to severe HS.

1.2 Purpose

The purpose of this study is to demonstrate superiority of secukinumab at Week 16, based on HiSCR rates versus placebo, along with the maintenance of efficacy of secukinumab at Week 52 in subjects with moderate to severe HS. Moreover, this study will assess the safety and tolerability of 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 efficacy of secukinumab compared to placebo with respect to HiSCR after 16 weeks of treatment.	● Achievement of HiSCR at Week 16. HiSCR is defined as at least a 50% decrease in Abscess and Inflammatory Nodule (AN) count with no increase in the number of abscesses and/or in the number of draining fistulae.

[redacted]

Objective(s)	Endpoint(s)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To demonstrate the efficacy of secukinumab compared to placebo after 16 weeks of treatment with respect to AN count ● To demonstrate the efficacy of secukinumab compared to placebo after 16 weeks of treatment with respect to: ● proportion of patients with HS flares ● proportion of patients with clinical response in HS related skin pain	● Percentage change from baseline in AN count at Week 16. ● Flaring up to Week 16. Flare is defined as at least a 25% increase in AN count with a minimum increase of 2 AN relative to baseline. ● Achievement of NRS30 at Week 16, among subjects with baseline NRS ≥ 3. NRS30 is defined as at least a 30% reduction and at least 2 unit reduction from baseline in Patient's Global Assessment of Skin Pain - at worst.
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
● To evaluate the safety and tolerability of secukinumab over 52 weeks of treatment.	● Clinical safety and tolerability assessments: ● physical exams, ● vital signs, ● laboratory assessments, ● AE monitoring
● To explore the long-term effect of secukinumab with respect to HiSCR, AN count, proportion of patients with flares, HS related skin pain up to 52 weeks of treatment.	● Achievement of clinical response as defined by HiSCR. ● Absolute and percentage change from baseline in AN count. ● Flares ● Achievement of pain relief as defined by NRS30.
● To evaluate the effect of secukinumab with respect to the following efficacy assessments: ● Modified Hidradenitis Suppurativa Score (mHSS); ● HS-Physician's Global Assessment (HS-PGA); ● Dermatology Life Quality Index (DLQI); ● Health Status Questionnaire (EQ-5D-3L); ● Patient Global Impression of severity (PGI-s); ● Patient Global Impression of change (PGI-c); ● Work Productivity and Activity Impairment (WPAI); ● HS Symptom Diary; ● Inflammatory markers with respect to CRP and ESR compared to placebo after 16 weeks and in the two secukinumab dose regimens up to 52 weeks of treatment.	● Absolute and percent change from baseline in modified Hidradenitis Suppurativa Score (mHSS). ● HS-PGA response. HS-PGA response is defined as the achievement of at least a 2-point reduction in HS-PGA score compared to baseline. ● DLQI response and absolute/percent DLQI total score change from baseline. DLQI response is defined as a decrease greater than 5.0 points from baseline. ● EQ-5D-3L Categories on Category questions and summary statistics on EQ -5D -3L score questions. ● Patient Global Impression of severity and change (PGI-s and PGI-c) categories. ● Absolute and percent change from baseline in Work Productivity and Activity Impairment - Specific Health Problem (WPAI-SHP). ● HS Symptom Diary items score change from baseline. ● Absolute and percent change from baseline in CRP and ESR
● To evaluate the pharmacokinetics of secukinumab in HS patients.	● AIN457 levels in serum
● To assess the development of immunogenicity against secukinumab.	● anti-AIN457 antibodies levels in serum
● To explore the potential association of biomarker levels with secukinumab efficacy and safety by visit up to Week 52 visit (EOT2).	● Biomarkers in serum

[redacted]

Objective(s)	Endpoint(s)
●To explore the efficacy of secukinumab compared to placebo with respect to HiSCR response after 16 weeks of treatment and the sustained efficacy over time in bio-naive patients.	● Achievement of HiSCR at Week 16 and up to Week 52 in bio-naive patients.
● To explore the efficacy of secukinumab compared to placebo with respect to HiSCR response after 16 weeks of treatment and the sustained efficacy over time in patients with body weight lower and higher than 90 kg (<90 kg and ≥90 kg).	● Achievement of HiSCR at Week 16 and up to Week 52 in patients with body weight lower and higher than 90 kg (<90kg and ≥90kg).

3 Study design

This is a multicenter, randomized, double-blind, placebo controlled, parallel group study with two secukinumab dose regimens in approximately 541 patients with moderate to severe HS.

The study consists of: Screening (up to 4 weeks), Treatment Period 1 (16 weeks) and Treatment Period 2 (36 weeks). Subjects who prematurely discontinue the study, or who complete the study and cannot or do not wish to continue in a planned optional extension study, will need to complete a post-treatment Follow-Up period (8 weeks).

Safety, efficacy, biomarker and pharmacokinetic measurements of secukinumab will be assessed.

An outline of the study design is presented in Figure 3-1, and a detailed visit and assessment schedule is provided in Table 8-1.

Screening (Screening to Randomization)

A screening period of up to 4 weeks will be used to assess the subject´s eligibility and to washout and/or taper prohibited medication(s). Two screening visits will be performed: Visit 1 (Day -28 to Day -14) and Visit 2 (Day -13 to Day -1). Subjects can be re-screened if the subject screen fails due to a transient medical condition or due to an insufficient prohibited medication washout period. Subjects can be re-screened only once and no study-related re-screening procedure should be performed prior to re-consenting the subject.

Important note:

In the event of a global health disruptive event, such as pandemic/epidemic affecting the ability of the patient or the site to adhere to protocol requirements and assessments, Investigators should only randomize patients if they expect them to be able to adhere to assessments and protocol-related activities. Evaluation of the eligibility of the subject should consider the ability to attend study visits and adhere to protocol assessments. If the latter is not anticipated, screening and randomization should not proceed, and re-screening (as allowable per protocol – see above) should be considered when conditions allow for proper trial management.

[redacted]

Treatment Period 1 (Randomization to Week 16 pre-dose)

Treatment Period 1 covers the time from randomization (baseline) through Week 16 (prior to Week 16 dosing). At baseline, eligible subjects will be randomized at a 1:1:0.5:0.5 ratio to one of four treatment arms:

- Secukinumab 300 mg every 2 weeks
- Secukinumab 300 mg every 4 weeks
- Placebo group to secukinumab 300 mg every 2 weeks
- Placebo group to secukinumab 300 mg every 4 weeks

Approximately 180 patients will be randomized to each of the two secukinumab regimen arms and another 180 patients will be randomized to two placebo switching to secukinumab regimen arms.

In the event of a global health disruptive event, such as pandemic/epidemic affecting the ability of the patient or the site to adhere to protocol requirements and assessments and therefore leading to a potential increase in the number of missing measurements, the Sponsor may consider recruiting additional patients to restore the sample size and maintain the pre-defined statistical power.

Randomization will be stratified by region, current antibiotic use and body weight. All subjects will receive a single s.c. injection of blinded study drug (active drug or placebo) once a week for four weeks (induction) at Baseline, Week 1, 2, 3 and 4. Thereafter, the frequency of study drug injections will be every 2 weeks for all subjects in order to maintain the treatment blind: either placebo (placebo to secukinumab arms), or secukinumab alternating with placebo every 2 weeks (secukinumab 300 mg every 4 weeks arm) or secukinumab every 2 weeks (secukinumab 300 mg every 2 weeks arm). See Figure 3-1.

In Treatment Period 1, home administrations **(H)** of study drug are scheduled at Weeks 6, 10 and 14.

Refer to Section 6.1.3 for further details on treatment arms.

Subjects who complete Treatment Period 1 will enter Treatment Period 2.

Treatment Period 2 (Week 16 post-dose to Week 52)

Treatment Period 2 is defined as the time from Week 16 (post-dose) through Week 52. From Week 16, all patients will receive secukinumab.

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

Subjects who were randomized to either of the two secukinumab regimens will continue on the same dose regimen. Subjects who were randomized to one of the two 'Placebo to secukinumab' regimens will receive either secukinumab 300 mg every 2 weeks or secukinumab 300 mg every 4 weeks.

At Week 16, all subjects will receive a re-induction consisting of a single s.c. injection of blinded study drug (active drug or placebo) once a week for four weeks, at Week 16, 17, 18, 19 and 20. Thereafter, all subjects will receive study drug injections every 2 weeks, either

[redacted]

secukinumab alternating with placebo every 2 weeks (secukinumab 300 mg every 4 weeks arm) or secukinumab every 2 weeks (secukinumab 300 mg every 2 weeks arm) until Week 50.

Home administrations **(H)** of study drug are scheduled at Weeks 22, 26, 30, 34, 38, 42, 46 and 50.

The planned end of Treatment Period 2 visit (EOT 2) will be performed at Week 52. At this visit, the site should call Interactive Response Technology (IRT) after performing the scheduled study assessments to record the completion of treatment period by subject(s). For subjects rolling over to the extension study, Week 52 will be the end of study visit; for subjects continuing to the Post-Treatment Follow-Up, the visit at Week 60 will be the end of study visit.

Subjects who discontinue study treatment prematurely for any reason other than withdrawal of informed consent before Week 52 should not be considered as discontinued from the study. Subjects should continue attending site visits for the study assessments. Subjects who are unwilling to continue attending further study visits after discontinuing the study drug, should attend the end of study visit. The End of Treatment visit (EOT 1 for discontinuation during Treatment Period 1 and EOT 2 for discontinuation during Treatment Period 2) which should be performed two weeks (where possible) after their last dose of study drug. After the EOT visit, subjects should enter the post-treatment Follow-Up period.

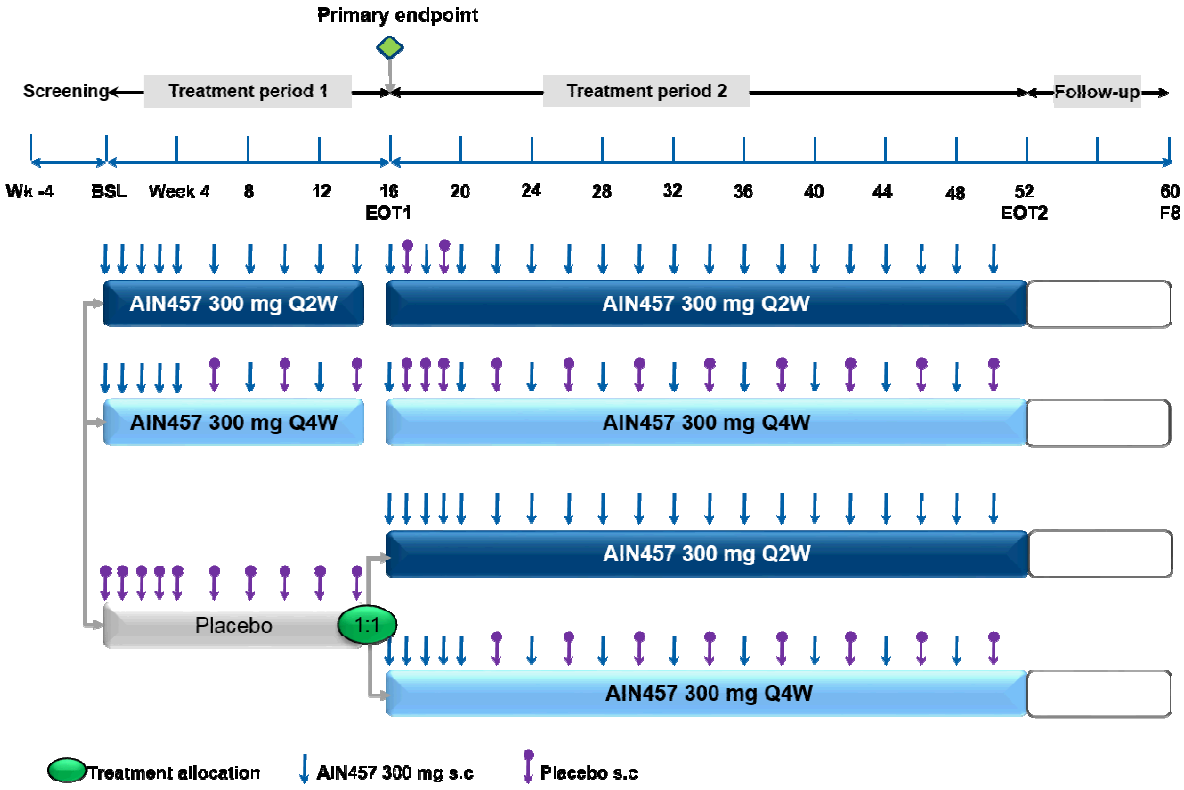
If the primary endpoint analysis conducted after all subjects complete Week 16 shows a positive benefit-risk for only one of the two dose regimens evaluated in the study (e.g. no significant effect on primary and secondary endpoints is observed for one of the proposed dose regimens), patients still participating in Treatment Period 2 will be transitioned to the dose regimen with positive benefit-risk.

Post-Treatment Follow-Up (8 weeks)

Only subjects who prematurely discontinue study treatment in Treatment Periods 1 or 2 for any reason, or subjects who do not enroll in the planned extension study, will enter the Post-Treatment Follow-Up and complete the Week 60 (F8) visit (see Table 8-1).

[redacted]

Figure 3-1 Study design



BSL: Baseline; EOT1/EOT2: End of Treatment 1/2; F8: End of Follow-up visit at Week 60;q2w: every two weeks; q4w: every four weeks. Treatment allocation for Placebo arm switching to secukinumab arms at Week 16 will be performed at the Randomization visit in 1:1 ratio and does not account for potential discontinuations during Treatment Period 1. Follow-up: only subjects who prematurely discontinue treatment during Treatment Period 1 or 2 or subjects who do not enroll in the extension study, will enter Follow-up.

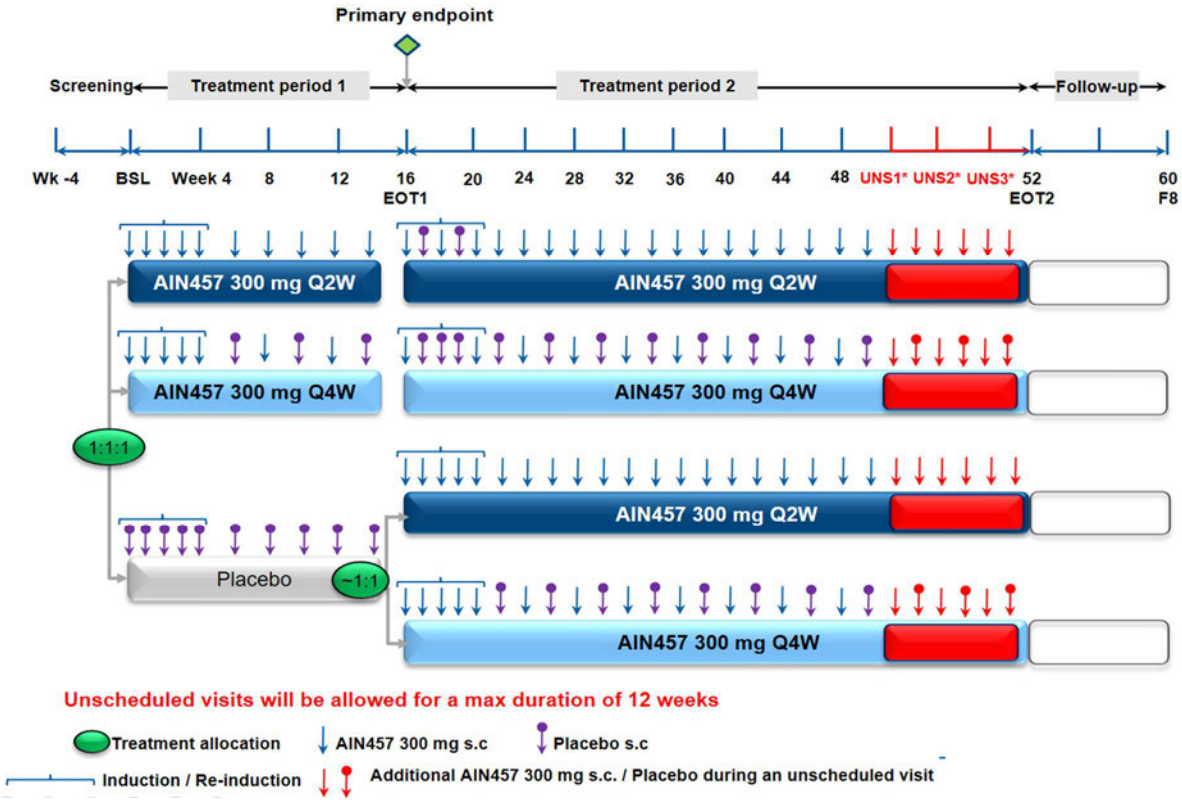
In the event of a global health disruptive event, such as a pandemic/epidemic (e.g. COVID-19), that limits or prevents the conduct of site study visits per protocol, special effort should be made to conduct on-site visits for the EOT(s) visits, Week 16 and Week 52. If it is not feasible to conduct these visits on site, virtual visits, or visits to the patient´s home should be attempted.

Delay of Week 52 visit (special scenario)

In the event Week 52 cannot be performed on-site as scheduled due to a global health disruptive event, such as a pandemic/epidemic (e.g. COVID-19), or to a delay of HAs/ECs approval of the extension protocol, an additional treatment period of up to a maximum of 12 weeks (i.e., up to 6 doses, the frequency of study drug injections will remain every 2 weeks) could be considered to ensure therapeutic continuity for the patients until they are able to perform Week 52 visit on-site, and then participate in the long-term extension study. See Figure 3-2.

[redacted]

Figure 3-2 Study design in case of global health disruptive event



*UNS = Unscheduled; UNS1, UNS2 and UNS3 correspond to three possible additional IRT calls at which 2 doses will be dispensed.

4 Rationale

4.1 Rationale for study design

The double-blind, randomized, parallel-group, placebo-controlled design will enable the evaluation of the benefit-risk of the two proposed secukinumab dose regimens in an adequate and well-controlled setting.

The primary and secondary endpoints reflect the most important domains in HS as proposed by the scientific community (Thorlacius et al 2018). The primary endpoint used in this study, HiSCR, was developed and validated in the context of the development program of adalimumab in HS. The HiSCR is considered to be adequately described and validated for its intended purpose as the primary endpoint in pivotal studies and has already been the basis for the HA approval of adalimumab as a treatment for patients with moderate to severe HS (Humira (adalimumab) EPAR).

AN count, number of flares and reduction in skin pain are selected as secondary endpoints due to their impact on patient's quality of life. These endpoints will provide complementary clinically relevant information not fully evaluated in the primary endpoint, HiSCR.

[redacted]

The primary endpoint will be evaluated at Week 16, which is the maximal acceptable duration of treatment exposure to placebo in this indication (see Section 4.3 for further rationale on the use of placebo). The total study duration including one year of treatment will allow for assessment of long-term safety and sustainability of the effect in the two dose regimens.

Adult subjects with moderate to severe HS will be included in the study. Moderate to severe HS will be defined as having at least 5 inflammatory lesions affecting at least 2 anatomical areas. This definition focuses on the degree and extent of inflammatory activity at baseline instead of using the level of scarring in the worst affected area as in the previously used Hurley Stages.

The proposed number of inflammatory lesions assures that patients would meet the definition of moderate to severe disease in the broadly used HS-PGA tool as proposed by Alavi (Alavi 2016). It is also in line with the proposed refined Hurley Staging (Horváth et al 2017), which proposes that selecting the population by requiring 5 inflammatory lesions in at least 2 anatomical locations is the appropriate way to define patients with moderate to severe HS who should be candidates for treatment with biologic anti-inflammatory therapies. Using this definition for moderate to severe HS it is expected that the study will mainly include patients in Hurley stages II and III, but will still allow a small proportion of patients with highly inflammatory Hurley stage I to enter the study. Based on available data, it is expected that the proportion of Hurley stage I patients in the proposed studies will be less than 15% of the recruited patients in this study.

Patient's previous treatment failure to antibiotics is not a requirement to enter the study. It is expected that the majority of the patients entering the study would have previously received systemic antibiotics at least during the period since diagnosis (≥ 1 year).

Reflecting the clinical practice in many countries and the concern of exposing some patients to placebo for up to 16 weeks without anti-inflammatory therapy, this study allows a proportion of the patients to remain on a stable dose of systemic antibiotics during Treatment Period 1. It is usually not considered acceptable to maintain patients on systemic antibiotics if they have previously failed to respond to this treatment approach. It is expected that patients who previously failed to respond to systemic antibiotics will enter the study without chronic use of systemic antibiotics (non-antibiotic strata). Information on the previous use of systemic therapies will be collected at baseline and will support efficacy analysis based on previous antibiotic use.

Patients with 20 or more fistulas at baseline will not be eligible for the study as the high level of scarring expected in these patients could significantly impair the ability to accurately count the number of inflammatory lesions for the primary and secondary endpoint.

4.2 Rationale for dose/regimen and duration of treatment

Two secukinumab dosing regimens will be evaluated in this study:

- Secukinumab 300 mg s.c. every 4 weeks
- Secukinumab 300 mg s.c. every 2 weeks

Both dose regimens will start with an induction period consisting of 300 mg s.c. injections at Baseline, Weeks 1, 2, 3, and 4, followed by the maintenance treatment as described in Section 3.

[redacted]

As clearly demonstrated in the development program for moderate to severe plaque psoriasis, it is expected that the induction period with weekly dosing during the first month will enable to quickly achieve effective drug concentrations and lead to a more rapid onset of clinical response.

Rationale for 300 mg s.c. every 4 weeks regimen

Secukinumab 300 mg s.c. with an initial weekly induction schedule up to 4 weeks followed by a s.c administration of every four weeks up to Week 48 is in line with the secukinumab Phase 3 registration program and the approved product labelling for moderate to severe plaque psoriasis. Initial information from case reports shows a positive clinical response to treatment in patients with HS treated with the psoriasis therapeutic dose (Thorlacius et al 2017; Schuch et al 2018). The demonstrated positive benefit-risk of the 300 mg s.c. every 4 weeks regimen in psoriasis, another inflammatory dermatological disease, supported by case reports showing positive clinical effects in HS patients indicates the potential of this dose regimen to show a positive benefit-risk in HS and justifies further evaluation in this study.

Rationale for 300 mg s.c. every 2 weeks regimen

In addition to the psoriasis dose regimen, the second dose regimen will be evaluated to achieve a higher exposure for the following reasons:

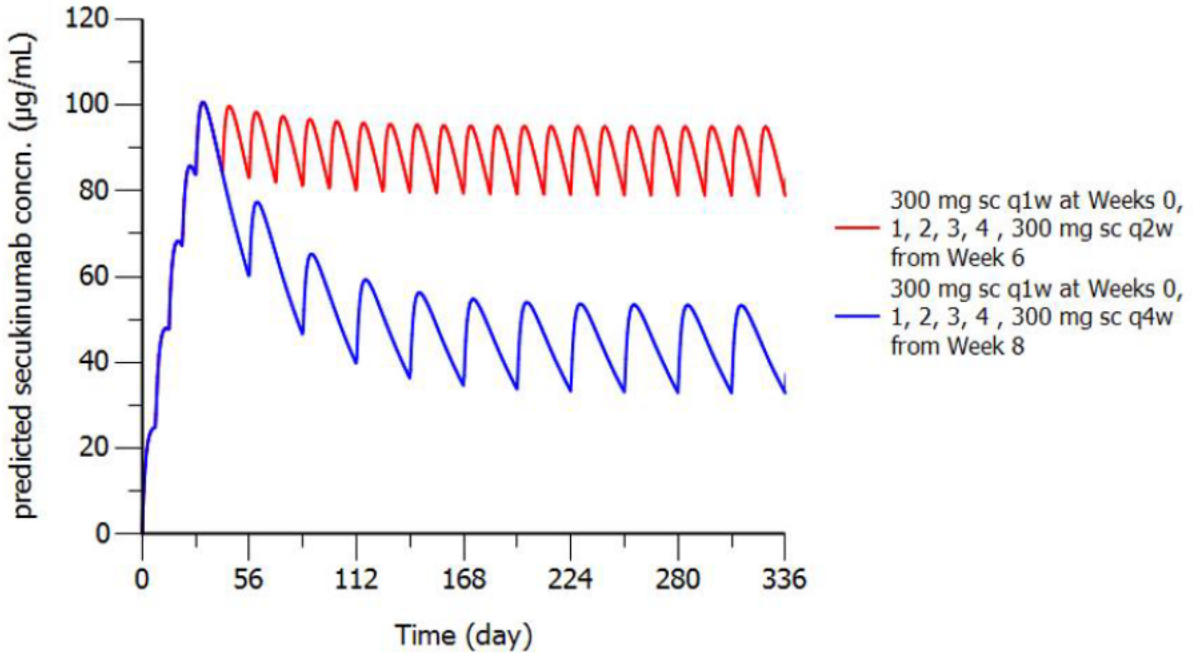
- Higher body weights are expected for this population compared to the psoriasis population (approximately 10 kg heavier weight for HS population in clinical trials (Kimball et al 2016)), thus potentially requiring higher doses to achieve adequate exposure. Secukinumab systemic exposure varies with body weight in an allometric relationship. For clearance, the allometric exponent was estimated to be close to 1; in other words, a doubling of body weight could lead to a nearly 2-fold increase in clearance and therefore reduced serum exposure (Bruin et al 2017). Therefore, evaluation of a dosing regimen with higher exposure than that resulting from the marketed regimen is appropriate in this heavier patient population.
- Higher local exposure than in psoriasis might be needed for this disease with deep inflammatory subcutaneous lesions.
- Clinical experience with adalimumab in HS supports a dosing regimen with higher exposure in HS than in psoriasis.

After the same induction period during the first month, considerably higher and more consistent systemic exposure can be achieved with a shortened dose interval (every 2 weeks) than can be reached with the 4 weeks interval (Figure 4-1).

Secukinumab 300 mg s.c. every 2 weeks has been tested in over 300 patients for at least 24 weeks in completed clinical studies in uveitis and psoriasis. A safety profile in line with that of secukinumab 300 mg s.c. every 4 weeks has been observed.

[redacted]

Figure 4-1 Predicted systemic exposure with 2 and 4 weeks dosing intervals during maintenance at the 300 mg dose level



Source: predicted PK profiles based on population PK model in psoriasis (Bruin et al 2017); Novartis data on file)

4.3 Rationale for choice of control drugs (comparator/placebo)

Placebo will be used as the comparator. Use of placebo as a control arm will minimize the number of patients that need to be exposed to a treatment which is without confirmed benefit-risk in HS at this stage. Demonstration of efficacy using either a superiority or non-inferiority design against an active drug would require a large potentially unfeasible sample size in an indication with such low prevalence.

[redacted]

Due to the concerns of keeping patients with HS on placebo, the use of placebo is limited to a maximum of 16 weeks. In addition, the risks to patients who are randomized to placebo will be minimized by allowing some patients to enter on systemic antibiotic therapy and by allowing rescue therapy with systemic antibiotics for those patients presenting with a clinically relevant increase of inflammatory lesions during the placebo period.

After 16 weeks, all patients originally randomized to placebo will then be switched to active drug in a blinded manner.

[redacted]

4.4 Purpose and timing of interim analyses/design adaptations

[redacted]

A primary endpoint analysis will be performed after all subjects have completed the visit at Week 16.

At the end of the study, the final analysis of all data collected will be performed when all subjects have completed their last study visit. All subjects, investigators/site personnel will remain blinded until final database lock.

[redacted]

4.5 Risks and benefits

Secukinumab has demonstrated positive benefit-risk in the treatment of multiple chronic inflammatory indications including moderate to severe plaque psoriasis, ankylosing spondylitis, psoriatic arthritis. Based on the available evidence at the time of this protocol (see Section 1.1 for further details), secukinumab has the potential to also show positive benefit-risk in reducing the extent of inflammation in patients with moderate to severe HS. Given the impact of these inflammatory lesions on the quality of life of patients with HS, a reduction in the number of such lesions could directly benefit patients.

Secukinumab therapy has a well-established and well-described safety profile based on extensive post-marketing experience and continued clinical trial patient exposure since its approval for the first indication of moderate to severe plaque psoriasis. Details of the risk and benefits are outlined in the current version of the Investigator's Brochure.

Observed risks at doses up to 300 mg s.c. every 4 weeks included infections, of which the most frequently reported were upper respiratory tract infections. Oral herpes, oral candidiasis and tinea pedis were also more frequently reported. Most of the infections were non-serious, mild to moderate in severity, clinically manageable and did not lead to treatment discontinuation. Neutropenia and hypersensitivity reactions are also risks observed with secukinumab. Cases of neutropenia were uncommon, generally mild to moderate, transient, did not lead to treatment discontinuation, and only a few cases were temporally associated with non-serious infections.

Secukinumab 300 mg s.c. every 2 weeks is not an approved dose regimen. It has been administered in 7 completed studies in approximately 460 patients with psoriasis and uveitis, with approximately 300 patients receiving continuous treatment for at least 24 weeks. This included over 200 patients with psoriasis. The safety profile observed in the available data is consistent with the known safety profile of secukinumab.

[redacted]

Treatment with multiple high doses of secukinumab (10 mg/kg and 30 mg/kg i.v.) has been administered to more than 2000 patients, with the majority receiving 3 doses of 10 mg/kg i.v. over 1 month and 38 patients receiving monthly doses for at least 6 months. Treatment with high doses (monthly exposure on chronic doses being approximately 2-fold higher compared to 300 mg s.c. every 2 weeks dose) was associated with a numerical increase in infections compared to placebo, mainly due to more reports of non-serious upper respiratory tract infections, but also a few more individual reports of non-serious local fungal infections such as oral or vulvovaginal candidiasis. Otherwise, the safety profile was consistent with the known safety profile of secukinumab with the approved doses.

The recently completed randomized, double-blind, multicenter study CAIN457A2324 (NCT03504852), evaluated the safety and efficacy of secukinumab 300 mg s.c. administered every 2 weeks (q2w) or every 4 weeks (q4w), in patients with psoriasis who weigh ≥90 kg. Study CAIN457A2324 showed that in psoriasis patients who weigh ≥90kg, secukinumab 300 mg q2w demonstrates a better treatment effect. Whilst the efficacy data is not yet published at the time of release of protocol amendment 02, the analysis of the safety data did not demonstrate any new safety signals with the q2w regimen and showed an overall safety profile in line with what is already known.

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, and periodic review of safety data by an independent DMC.

Based on all available data, and a positive benefit/risk ratio for the treatment of moderate to severe HS with secukinumab at doses 300 mg q4w and 300 mg q2w, it is appropriate to initiate study CAIN457M2302.

Additional information can be found in the IB for secukinumab.

5 Population

The study population will consist of a representative group of adult male and female patients (≥ 18 years old) with moderate to severe HS. The study originally aimed to randomize approximately 471 patients in approximately 132 study sites worldwide. To account for the disruptive impact of the COVID-19 pandemic on the conduct of the study since the release of protocol amendment 01, the number of randomized patients was increased to approximately 541 (15% increase from the original population of 471 patients). Up to 40% of the patients will be allowed to enter the study on treatment with stable dose of antibiotics. Patients who drop out after they have been randomized will not be replaced.

In case of a global health disruptive event, such as pandemic/epidemic impacting the conduct of the trial, patients or sites may not be able to perform the assessments as per protocol, leading to a potential increase in the number of missing measurements. If the latter should affect the power of tests and the precision of estimates for this study, the Sponsor may consider recruiting additional patients to restore the sample size and maintain the pre-defined statistical power.

5.1 Inclusion criteria

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

[redacted]

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients ≥ 18 years of age.
3. Diagnosis of HS ≥ 1 year prior to baseline.
4. Patients with moderate to severe HS defined as:
   - A total of at least 5 inflammatory lesions, i.e. abscesses and/or inflammatory nodules

   AND
   - Inflammatory lesions should affect at least 2 distinct anatomic areas
5. Patients agree to daily use of topical over-the-counter antiseptics on the areas affected by HS lesions while on study treatment.

5.2 Exclusion criteria

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

1. Total fistulae count ≥ 20 at baseline.
2. Any other active skin disease or condition that may interfere with assessment of HS.
3. Active ongoing inflammatory diseases other than HS that require treatment with prohibited medications (see Table 6-2).
4. Underlying conditions (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal such as inflammatory bowel disease) which in the opinion of the investigator significantly immunocompromises the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy.
5. Current severe progressive or uncontrolled diseases which renders the patient unsuitable for the trial or puts the patient at increased risk, including any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
6. Use or planned use of prohibited treatment. Washout periods detailed in the protocol have to be adhered to (see Table 6-2).
7. For patients enrolling in the non-antibiotic strata: use of systemic antibiotics for the treatment of HS within 28 days before baseline.

   For patients enrolling in the antibiotic strata: patients enter the study under concomitant treatment with systemic antibiotics (as per protocol) on a stable dose (defined as a dose or dose regimen that has not changed in the previous 28 days before baseline and is considered unlikely to change at least for the first 16 weeks during the study).
8. History of hypersensitivity to any of the study drug constituents.
9. Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 A/F or the IL-17 receptor.
10. History of chronic or recurrent systemic infections or active systemic infections during the last two weeks (exception: common cold) prior to randomization.
11. 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

[redacted]

evidence of active tuberculosis. 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 was completed at least four weeks before randomization.

12. Medical history record of infection with human immunodeficiency virus (HIV), hepatitis B or C prior to randomization, except for hepatitis C successfully treated and cured.
13. 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 keratoses 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).
14. History or evidence of ongoing alcohol or drug abuse, which in the opinion of the investigator will prevent the patient from adhering to the protocol and completing the study.
15. Pregnant or lactating women.
16. 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 bilateral 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). For United Kingdom: with spermicidal foam/gel/film/cream/vaginal suppository.
    - 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 bilateral tubal ligation

[redacted]

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.

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

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	Blinding/volume	Sponsor (global or local)
Secukinumab 300 mg	Solution for injection	Subcutaneous Use	Double blinded subject packs; 2 ml pre-filled syringe	Sponsor (global)
Placebo	Solution for injection	Subcutaneous Use	Double blinded subject packs; 2 ml pre-filled syringe	Sponsor (global)

Novartis will supply the investigational therapy as follows:

- Secukinumab 300 mg solution for sub-cutaneous injection in a 2 ml pre-filled syringe
- Placebo solution for sub-cutaneous injection in a 2 ml pre-filled syringe

Each placebo pre-filled syringe contains a mixture of inactive excipients, matching the composition and the appearance of the secukinumab 300 mg dose.

Secukinumab and the secukinumab matching placebo will be labeled as "AIN457 300 mg / Placebo" (2 ml) to keep the blind. Subjects will be initially instructed about injections by site staff. They will also receive instructions on how to self-inject using the pre-filled syringe.

6.1.2 Additional study treatments

No additional treatment beyond investigational drug and control drug are included in this trial. Subjects are requested to use over-the-counter antiseptics according to eligibility criteria, Section 6.2.1 and Section 6.2.2. For rescue medication, see Section 6.2.3.

6.1.3 Treatment arms/group

At Baseline/Randomization visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) in a 1:1:0.5:0.5 ratio to one of the following 4 treatment groups:

• **Secukinumab 300 mg every 2 weeks group:** subjects will receive a loading dose of secukinumab 300 mg once weekly for four weeks (at Randomization, Weeks 1, 2, 3 and 4), followed by secukinumab 300 mg every two weeks, starting at Week 6 and up to Week

[redacted]

50. These subjects will receive two additional placebo injections at Weeks 17 and 19 to maintain the treatment blind during the re-induction.

• **Secukinumab 300 mg every 4 weeks group:** subjects will receive secukinumab 300 mg once weekly for four weeks (at Randomization, Weeks 1, 2, 3 and 4), followed by secukinumab 300 mg every four weeks, starting at Week 8 and up to Week 48. In order to maintain the treatment blind, subjects in this group will also receive a placebo injection every 4 weeks starting at Week 6, until Week 50. These subjects will receive three additional placebo injections at Weeks 17, 18 and 19 to maintain the treatment blind during the re-induction.

• **Placebo group to secukinumab 300 mg every 2 weeks:** subjects will receive placebo once weekly for four weeks (at Randomization, Weeks 1, 2, 3 and 4), followed by placebo every two weeks, starting at Week 6 and up to Week 14. At Week 16, subjects will be switched from Placebo to Secukinumab 300 mg every 2 weeks. The subjects will receive secukinumab 300 mg once weekly for four weeks (Weeks 16, 17, 18, 19 and 20), followed by secukinumab 300 mg every two weeks, starting at Week 22 and until Week 50.

• **Placebo group to secukinumab 300 mg every 4 weeks:** subjects will receive placebo once weekly for four weeks (at Randomization, Weeks 1, 2, 3 and 4), followed by placebo every two weeks, starting at Week 6 and up to Week 14. At Week 16, subjects will be switched from Placebo to Secukinumab 300 mg every 4 weeks. The subjects will receive secukinumab 300 mg once weekly for four weeks (Weeks 16, 17, 18, 19 and 20), followed by secukinumab 300 mg every four weeks, starting at Week 24 and up to Week 48. To maintain the treatment blind, subjects will receive placebo alternating with secukinumab starting at Week 22 and up to Week 50.

See Figure 3-1 for graphical representation of type of injection per treatment group and visit.

6.1.4 Treatment duration

The planned duration of treatment is 52 weeks. Subjects may be discontinued from treatment earlier due to unacceptable toxicity or at the discretion of the investigator or the subject. After completion of Treatment Period 2, subjects may continue treatment in a planned extension study or enter the 8-week post-treatment Follow-up in this study.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator must instruct the subject to notify the study site about any new medications taken after enrolling in the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate electronic case report/record form (eCRF).

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.

[redacted]

6.2.1.1 Permitted concomitant therapy

Antiseptic Therapy

Subjects should be instructed to use daily topical over-the-counter antiseptics on the skin areas affected by HS lesions following the local standard practice.

Wound Care

Concomitant use of wound care dressings on HS wounds is allowed following the local standard practice.

6.2.1.2 Permitted concomitant therapy requiring caution and/or action

Antibiotics

Systemic antibiotics for the treatment of acute systemic infectious disease both related or unrelated to HS (e.g. pneumonia, cellulitis) are allowed as medically warranted during the study.

Systemic antibiotics for the treatment of HS are only allowed as rescue medication as described in Section 6.2.3 below.

For subjects entering the study in the antibiotic strata, treatment with the following tetracyclines on a stable dose is allowed in Treatment Period 1:

- Tetracycline up to 500 mg twice a day
- Minocycline up to 100 mg twice a day
- Doxycycline up to 100 mg twice a day

Analgesics

Subjects will be required to wash out opioid analgesics (including tramadol) for 14 days prior to Baseline. This includes opioids for both HS-related pain and non-HS-related pain.

Subjects on a stable dose of a non-opioid analgesic ("as needed" is not considered stable) may continue the analgesic, provided the dose is stable for 14 days prior to Baseline and is anticipated to remain stable for at least 16 weeks of treatment.

In case a subject presents with uncontrolled pain related to HS during the study, ibuprofen and acetaminophen (paracetamol) are permitted.

If HS-related pain is uncontrolled with ibuprofen or acetaminophen (paracetamol) at the maximal dose as per local label during the trial, subjects can be prescribed tramadol (at a dose of up to 100 mg orally every 4 hours), not to exceed 400 mg/24 hours.

Information on the concomitant use of analgesics should be recorded by the subject in the eDiary and reviewed by the investigator at the scheduled visits.

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-2 that could confound the efficacy assessment or could put the patient at an additional safety risk are not allowed during the study and wash-out

[redacted]

periods for these treatments prior to randomization are indicated in the table. If the use of these treatments is required, then the subject should not be randomized.

The investigator should instruct the subject to notify the study site about any new treatments he/she takes after the start of study treatment. All prohibited medications and significant non-drug therapies administered after the subject starts study treatment must be recorded in the eCRF.

If a prohibited treatment listed in Table 6-2 is used during the study, the subject should discontinue use of the prohibited treatment if he/she wishes to continue in the study. At the discretion of the investigator, if the subject's use during the study of a prohibited treatment presents undue safety risk for the subject, the subject should be discontinued from study treatment.

Table 6-2 Prohibited medication

Medication	Prior to randomization	Use between randomization and last dose of study drug	Action taken
Prior treatment with secukinumab or other agents blocking IL-17 A/F or IL-17R	Not allowed	Not allowed	Subject not eligible
Systemic biological immunomodulating treatment (e.g. adalimumab, infliximab, ustekinumab, anakinra, natalizumab)	12 weeks wash-out period or 5 half-lives, whichever is longer	Not allowed	Discontinue use or discontinue study treatment
Systemic non-biologic immunomodulating treatment (e.g. methotrexate (MTX), cyclosporine A, retinoids, apremilast)	28 days wash-out period required	Not allowed	Discontinue use or discontinue study treatment
Topical antibiotic therapies for the treatment of HS	14 days wash-out period required	Not allowed until Week 16	Discontinue use or discontinue study treatment if not medically warranted
Antibiotics for the treatment of HS (non-antibiotic strata)	28 days wash-out period required	Not allowed until Week 16, except for rescue treatment	Discontinue use or discontinue study treatment if not medically warranted
Systemic corticosteroids for the treatment of HS	28 days wash-out period required	Not allowed	Discontinue use of discontinue study treatment
Opioid analgesics	14 days wash-out period required	Not allowed	Discontinue use or discontinue study treatment
Surgeries for the treatment of HS other than allowed as rescue therapy	Not allowed within 6 weeks prior to randomization	Not allowed until Week 16	Discontinue study treatment

[redacted]

Medication	Prior to randomization	Use between randomization and last dose of study drug	Action taken
Live vaccines	Not allowed within 6 weeks prior to randomization	Not allowed	Discontinue study treatment
Any investigational treatment or participation in any interventional trial	28 days or 5 half-lives (whichever is longer) wash-out period required	Not allowed	Discontinue study treatment

6.2.3 Rescue medication

Antibiotics

At Week 4, 8 and 12, if a subject experiences an increase in their AN count (for example, the total count is greater-than-or equal-to 150% of the weighted average of screening and baseline AN count (Section 12.4.1)) with a minimum increase of 3 lesions, oral antibiotics rescue medication can be used. This applies only to Treatment Period 1.

Subjects who qualify for rescue medication may initiate antibiotic treatment with minocycline or doxycycline up to 100 mg bid. The dosing regimen must remain stable until Week 16. Except for current antibiotic use strata, concomitant use of antibiotic therapy for treatment of HS is otherwise not allowed. However, antibiotics are permitted to treat an acute infection if medically warranted (Section 6.2.1.2). Rescue antibiotic therapy should be captured in the source and on the appropriate eCRF.

Lesion Intervention

In the event of an acutely painful single lesion that requires an immediate intervention, the investigator will be allowed to perform an unplanned surgery/intervention for lesion such as excision, drainage or intra-lesion steroid administration at any time.

Other HS related surgery is not allowed until after Week 16.

All study visit evaluations must take place before any interventions are performed.

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 patient is enrolled for screening and is retained for the subject throughout his/her participation in the trial. A new Subject No. will be assigned if the subject is rescreened. 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 participation is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available within the electronic data capture (EDC) system.

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

[redacted]

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

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 package of study drug to be dispensed to the subject. The randomization number will not be communicated to the investigator or his/her delegate.

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 patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient 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 Clinical Drug Supply using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by region, concomitant antibiotic use (Yes/No) and body weight (weight < 90kg / ≥ 90kg).

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

6.4 Treatment blinding

This is a double blind study. Subjects, investigator staff, persons performing the assessments, and Novartis 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 vendors whose role in trial conduct requires their unblinding (e.g., IRT)
- Drug Supply Management
- The 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 treatment that are all identical in packaging, labeling, schedule of administration, appearance and schedule of administration.

The randomization codes associated with subjects from whom PK samples are taken will be disclosed to the bioanalyst and pharmacokineticist (if required at primary endpoint analysis) who will keep serum concentrations confidential until database lock.

For subjects, investigators/site personnel and Novartis personnel working directly with the sites, unblinding will occur in the case of subject emergencies (see Section 6.6.3), and at the conclusion of the study. The appropriate personnel from the study site and Novartis will assess

[redacted]

whether the study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

At the time of a primary endpoint analysis after all subjects have completed Week 16, the designated Novartis personnel (e.g. biostatisticians and programmers involved in the analysis, key Global Team members) may have access to the unblinded results. Field monitors/clinical research associates will remain blinded until after final database lock. Subjects and site personnel directly involved in the conduct of the trial, i.e. investigator staff and persons performing the assessments, will remain blinded to individual treatment allocation until the conclusion of the study to ensure study integrity is maintained.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

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

Not applicable.

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. Compliance will be assessed by the investigator and/or study personnel at each visit using empty medication packaging, pre-filled syringe (PFS) and information provided by the subject. This information should be captured in the source document at each visit. 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 is responsible for treatment dispensation, administration and accountability. Cross-checks should be performed for home administrations (H) and empty medication outer packing and patient's returned PFS should be collected for compliance checks by field monitors.

[redacted]

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with secukinumab, as detailed in the Pharmacokinetics Section 8.5.2.

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.

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 at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- subject number

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

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

6.7 Preparation and dispensation

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 case of a major health care event (e.g., pandemic, epidemic) that limits or prevents on-site study visits, if required alternative ways to provide study drug may be implemented, including but not limited to shipping or home delivery for home administration. The shipment/provisioning should cover an adequate period, based on local situation and regulations. In this case, regular phone calls or virtual contacts (approximately every 4 weeks, prior to home administration, or more frequently if needed) will occur between the site and the

[redacted]

subject for instructional purposes, safety monitoring and discussion on patient's health status until the subject can again visit the site.

This is necessary to ensure that there are no safety concerns to the subject requiring treatment interruption or discontinuation.

The subjects will be supplied with material to document drug self-administration and to allow accountability of the study medication. At the site level, the agreement with/approval of the Principal Investigator, Ethics Committee/ Institutional Review Board (EC/IRB) and any other Board as appropriate should be in place to implement home delivery.

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. 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. The subjects will record the date(s) of administration at home on a diary and will return the used medication and packaging at their next visit to the site. Site staff will record in the appropriate documents the dates of the administration. Detailed instructions will be provided separately. 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 require one box with PFS per dose throughout the study:

- One secukinumab 300 mg, 2ml PFS **OR**

[redacted]

- One secukinumab placebo 300 mg, 2ml PFS.

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 study scheduled 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. At Week 1, subjects will be asked to refer to the IFU and to proceed with self-injection of the actual study drug (i.e. without a detailed explanation/instruction on handling the syringe).

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.

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.

In case of a major health care event (e.g., pandemic, epidemic) that limits or prevents on-site study visits, home administration of the study drug could be generally permitted. Home administration can be performed by the subject 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 subject 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 subject or caregiver should be made as to whether this constitutes sufficient training and oversight.

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 30 to 45 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.

[redacted]

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 and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) and CDS. 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 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 for the duration of the study. If there is any question that the subject will not reliably comply, they must not be entered in the study.

The study includes optional sub-study (biopsy sampling) / DNA component which requires a separate signature if the subject agrees to participate. It is required as part of this protocol that the Investigator presents this option to the subjects, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional assessments (DNA / biopsy sampling substudy) 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 after IRB/IEC approval.

Subjects might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

During a major health care disruption (e.g., pandemic, epidemic) that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone,

[redacted]

videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial subject and person obtaining informed consent, etc).

8 Visit schedule and assessments

Table 8-1 lists all of the study visits and indicates with an "X" when the assessments are to be performed. An 'S' indicates the data for that assessment are in the source documents at the site.

Subjects should be seen for all visits on the designated day or as close as possible to the original planned visit schedule.

If for any reason the subject is a screen failure, the subject may be rescreened once only.

If a subject rescreens for the study, then 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. 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 test performed by the central laboratory.

During the treatment periods, subjects may be seen at an unscheduled visit, e.g., if they experience deterioration of HS, 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.

Subjects who discontinue study treatment will continue to be followed up for as long as possible, and efforts should be made so that subjects continue study visits as per the assessment schedule even if not on study drug. Special effort should be made up until Week 16 to ensure that those subjects who prematurely discontinue study treatment attend all scheduled visits.

Subjects who discontinue study treatment before completing the study and do not wish to attend site visits for assessments only should be scheduled for an end of study visit 2 weeks (wherever possible) after their last study treatment administration, at which time all the assessments listed for EOT 1 (Week 16)/EOT 2 (Week 52) will be performed. Subjects should then return to the study site 8 weeks after completing EOT visit at Week 60 Follow-Up visit for final safety and efficacy assessments.

If a subject refuses to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone or by sending appropriate correspondence (i.e. certified letter) immediately. At this contact, the safety (e.g., potential occurrence of AE or SAE) and the primary reason for a subject's premature withdrawal should be determined.

At a minimum, subjects who pre-maturely discontinue the treatment will be contacted for safety evaluations during the 10 weeks following the last dose of study treatment, including final

[redacted]

contact at the 10 week point. Documentation of attempts to contact the subject should be recorded in the subject record.

It is recommended that assessments be completed in the following order: PROs, Physician assessments, study visit procedures (e.g. laboratory and PK sample collection, vital signs measurements), study treatment administration.

In the event of a major health care event (e.g., pandemic, epidemic) that limits or prevents on-site study visits, regular phone calls (approximately 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 case report form (e.g., AE, procedure) should be entered as appropriate. Special effort should be made to collect information related to EOT 1, (Week 16) and EOT 2 (Week 52) visits. If it is not feasible to conduct these visits on-site, phone calls should be attempted instead. Additional Unscheduled doses could be given at Home after Week 50 every 2 weeks for a maximum of 12 weeks until the subject is able to perform the Week 52 visit on-site.

Table 8-1 Assessment Schedule

Period	Screening		Treatment Period 1								Treatment Period 2												Post-Treatment Follow-Up
Visit Name	Screening 1	Screening 2	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16 / EOT1	Week 17	Week 18	Week 19	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	UNS 1 to 3	Week 52 / EOT2	Week 60 / F8
Days	-28 to -14	-13 to -1	1	8	15	22	29	57	85	113	120	127	134	141	169	197	225	253	281	309	337		365	421
Obtain informed consent (ICF)	X																							
Demography	X																							
Inclusion / Exclusion criteria[1]	X	X	X																					
Washout evaluation / instruction	S	S	S																					
Relevant medical history / current medical condition	X																							
HS medical history and previous therapies	X																							
Smoking history	X																							
Hurley stage	X		X						X	X													X	
Prior / concomitant medications[2]	X	Update as necessary																						
Adverse Events[3]	X	Update as necessary																						
Physical Examination[1]			S							S													S	S
Body Height	X																							
Body Weight	X		X				X			X					X								X	
Vital Signs	X		X				X	X	X	X				X	X	X	X	X	X	X	X		X	X
Tuberculosis test	X																						X	

[redacted]

Period	Screening		Treatment Period 1								Treatment Period 2													Post-Treatment Follow-Up
Visit Name	Screening 1	Screening 2	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16 / EOT1	Week 17	Week 18	Week 19	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	UNS 1 to 3	Week 52 / EOT2	Week 60 / F8
Days	-28 to -14	-13 to -1	1	8	15	22	29	57	85	113	120	127	134	141	169	197	225	253	281	309	337		365	421
Lesion count (physician)	X	X	X		X		X	X	X	X		X		X	X	X	X	X	X	X	X		X	X
Flare assessment[4]	X	X	X		X		X	X	X	X		X		X	X	X	X	X	X	X	X		X	X
Numerical Rating Scale for pain assessment[5]	Completed daily in the eDiary										Completed weekly in the eDiary													
Modified Hidradenitis Suppurativa Score (mHSS)			X						X	X													X	
HS-Physician's Global Assessment			X		X		X	X	X	X						X							X	
Patient's Lesion Count	Completed weekly in the eDiary																							
DLQI			X		X		X		X	X						X							X	
EQ5D			X		X		X		X	X						X							X	
Patient Global Impression of severity (PGI-s)			X		X		X		X	X						X							X	
Patient Global Impression of change (PGI-c)			X		X		X		X	X						X							X	
Work productivity Activity Impairment (WPAI)			X		X					X						X				X			X	
HS Symptom Diary[6]	Completed daily in the eDiary													X	X	X				X			X	
Hematology	X		X		X		X	X	X	X		X		X		X				X			X	X
Clinical Chemistry	X		X		X		X	X	X	X		X		X		X				X			X	X

[redacted]

Period	Screening		Treatment Period 1								Treatment Period 2												Post-Treatment Follow-Up
Visit Name	Screening 1	Screening 2	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16 / EOT1	Week 17	Week 18	Week 19	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	UNS 1 to 3	Week 52 / EOT2	Week 60 / F8
Days	-28 to -14	-13 to -1	1	8	15	22	29	57	85	113	120	127	134	141	169	197	225	253	281	309	337		365	421
Fasting lipid panel			X							X													X	
Urinalysis	X		X																				X	
Serum pregnancy test	X																							
Urine pregnancy test			S				S	S	S	S				S	S	S	S	S	S	S	S	S	S	S
Blood sample for pharmacokinetics			X							X					X								X	X
Blood sample for immunogenicity			X							X													X	X
Biomarker serum			X							X													X	
Optional biopsy sample[7]			X							X													X	
Optional DNA sampling[8]			X																					
Contact IRT	S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
Randomization			X																					
Drug dispensation[9]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dose administration[10]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Period completion/disposition form			X							X													X	
Health care resource utilization					X				X	X						X							X	
Trial Feedback Questionnaire (optional)			X													X							X	

[redacted]

Period	Screening		Treatment Period 1								Treatment Period 2												Post-Treatment Follow-Up
Visit Name	Screening 1	Screening 2	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16 / EOT1	Week 17	Week 18	Week 19	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	UNS 1 to 3	Week 52 / EOT2	Week 60 / F8
Days	-28 to -14	-13 to -1	1	8	15	22	29	57	85	113	120	127	134	141	169	197	225	253	281	309	337		365	421

[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] These assessments are source documentation only and will not be entered into the eCRF. However, data regarding to which inclusion/exclusion criteria are not met are captured on the Inclusion/Exclusion eCRF.
[2] While all concomitant medications are recorded on eCRF, patients will record their daily analgesics use on eDiary.
[3] AEs /SAEs occurring after the patient has provided informed consent must be reported.
[4] Occurrence of flare will be calculated from lesion count assessment and does not require any additional action from the site staff.
[5] Subjects will complete the NRS skin pain assessment using eDiary. From Screening through Week 16, subjects will complete a daily diary of their skin pain. From Week 16 through Week 52, subjects will complete skin pain assessments on a weekly basis.
[6] Instruct the subject on the use of the patient eDiary. From Screening through Week 16, subject will complete the diary on a daily basis. From Week 16 through Week 52, subjects will complete the diary at Week 20, 24, 28, 44, 52.
[7] Optional biopsy sample must only be collected after separate informed consent is signed at sites participating in the lesion biopsy substudy
[8] Optional blood sample for DNA sampling can only be collected after separate informed consent is signed
[9] After all assessments are completed, study site personnel should access IRT and dispense study treatment
[10] Home administrations will be performed at Weeks 6, 10, 14, 22, 26, 30, 34, 38, 42, 46 and 50. In case of a major global health event, additional home administrations can be performed between Week 50 and Week 52. Home administrations can be performed by subject or 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.

[redacted]

8.1 Screening

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. For each subject who has signed informed consent and discontinued before entering the double-blind treatment period, IRT must be notified within 5 days and the reason for not being randomized will be entered on the disposition eCRF. In addition, the Screening visit date, the Demography eCRF, Informed Consent eCRF, Inclusion/Exclusion Criteria eCRF and Subject rescreening eCRF (for rescreened subjects) must be completed.

Adverse events that are not SAEs will be followed up by the investigator and collected only in the source data. However, serious adverse events should be recorded in the eCRF for any serious adverse event (SAEs) that occurred during the screening period. If consent was withdrawn during the screening period before the subject was randomized, complete the appropriate eCRF.

8.2 Subject demographics/other baseline characteristics

8.2.1 Demography

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

8.2.2 HS medical history/diagnosis

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

- The date of first symptoms
- The date of first diagnosis of HS
- HS family history

8.2.3 Prior HS medications and therapy

Any treatments for HS since initial diagnosis (as determined through medical history records or through subject interview) prior to study entry will be collected and recorded in the eCRF (including previous use of antibiotics, non-biologic immunomodulators and biologic therapies), along with the duration of the prior therapy and the reason for discontinuation.

8.2.4 Hurley stage

The Hurley staging system is a severity scale that assesses both current activity and past scarring, ranging from isolated abscesses in the primary stage to coalescing lesions with scarring and sinus tracts in the tertiary stage (Table 8-2). Hurley stage will be recorded in eCRF.

[redacted]

Table 8-2 Hurley stages

Stage	Description
I	Abscess formation, single or multiple without sinus tracts and cicatrization/scarring
II	Recurrent abscesses with tract formation and cicatrization. Single or multiple, widely separated lesions
III	Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across entire area

8.2.5 Smoking History

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

8.2.6 Relevant 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.

8.2.7 Prior and concomitant medications

Concomitant medications and prior medications taken over the 6 months preceding study enrollment for reasons other than HS will be captured at the screening visit, and updated as necessary in the relevant eCRF. In addition, information on the concomitant use of analgesics should be recorded by the subject in the eDiary and reviewed by the investigator at the scheduled visits.

8.2.8 Determination of the tuberculosis status

Determination of the 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, TB testing (QuantiFERON-TB Gold assay). Any significant findings should be recorded in the eCRF.

QuantiFERON TB-Gold In-Tube assay

A QuantiFERON® TB-Gold In-Tube assay (QFT) to screen a population for latent tuberculosis infection (Doherty et al 2008) will be used at Screening to evaluate the subjects' eligibility for the study. 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 QuantiFERON®-TB Gold 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.

[redacted]

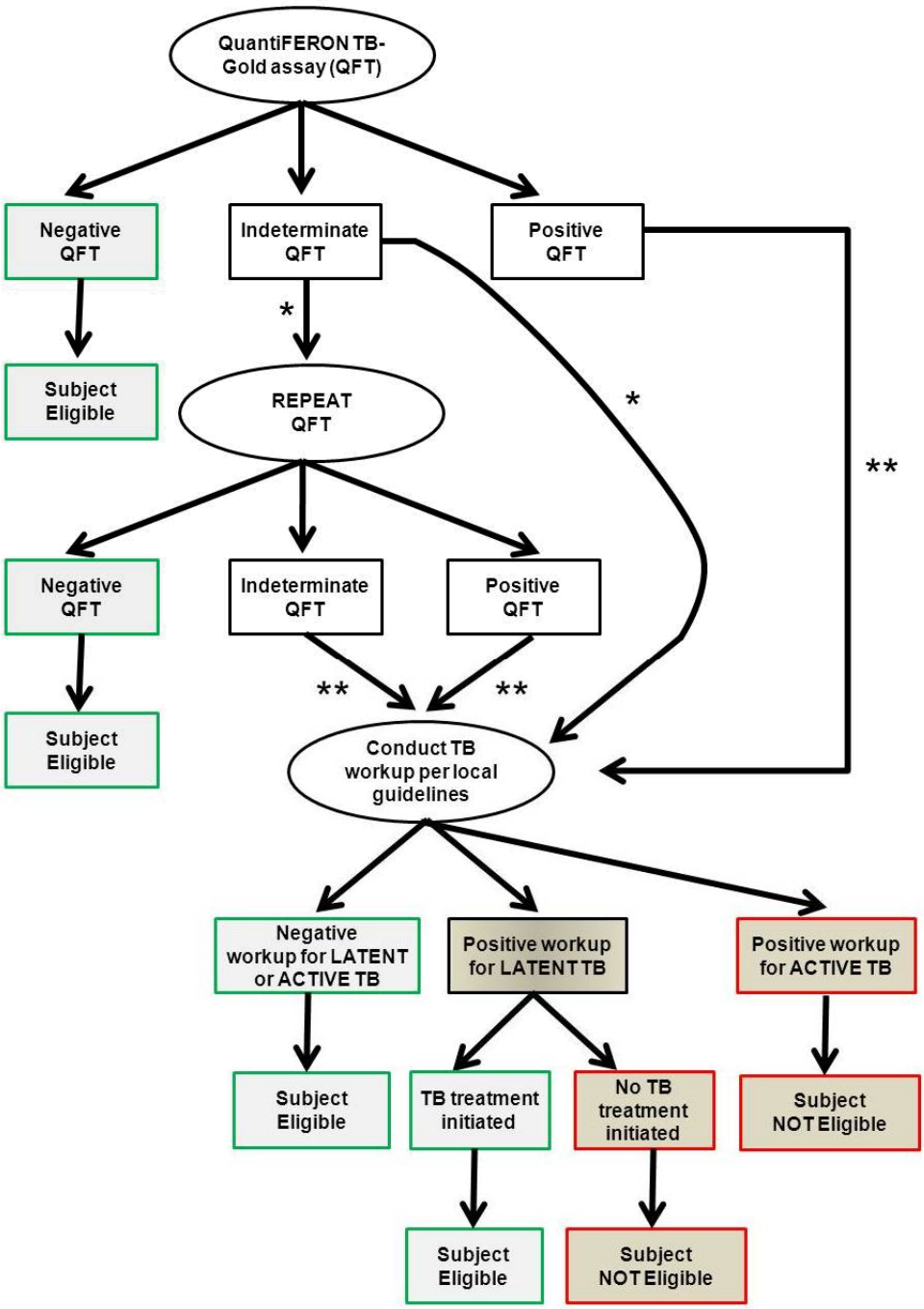
The workflow of sample handling in case of positive or indeterminate test results is provided in Figure 8-1.

- If the test result is **negative**, the subject may be randomized.
- 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 completed at least four weeks before randomization.
  - 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.
- 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.
  - If the second test is negative, the subject may be randomized.
  - If the second test is positive, the investigator should perform work-up as per local guidelines. 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 completed at least four weeks before randomization. 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.
  - If the second test is again indeterminate, the investigator should perform follow-up for the test result as per local procedures. Subjects tested 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. Subjects positive for **active** TB per work-up are not eligible for the study. Subjects negative for TB per work-up (no signs of latent or active TB) may be randomized to the trial if the work-up 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 Epoch (within 4 weeks prior to randomization) and TB work-up will only be considered if it was completed **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 completed at least four weeks before randomization. Subjects positive for active TB per work-up are not eligible for the study. Subjects negative for TB per work-up (no signs of latent or active TB) may be randomized to the trial.

[redacted]

Figure 8-1 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 assay (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 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).

[redacted]

8.3 Efficacy

Whenever possible, efficacy assessments for an individual subject should be performed by the same member of the study site staff throughout the study.

In the event of a pandemic/epidemic that limits or prevents on-site study visits, selected efficacy assessments (excluding lesion count) can alternatively be done via phone calls, virtual contacts or visits of site staff to the subject´s home, depending on local regulations and capabilities.

Efficacy assessments based on Patient Reported Outcomes (PROs) might alternatively be done remotely from the subject´s home (e.g. online or by telephone interview), depending on local regulations and technical capabilities.

8.3.1 Hidradenitis Suppurativa Clinical Response (HiSCR)

The HiSCR (Kimball et al 2014) is defined by the status of three types of lesions: abscesses (fluctuant, with or without drainage, tender or painful), inflammatory nodules (tender, erythematous, pyogenic granuloma lesion), and draining fistulas (sinus tracts, with communications to skin surface, draining purulent fluid). The definition of responders to treatment (HiSCR achievers) is:

- at least a 50% reduction in abscesses and inflammatory nodules (ANs),
- no increase in the number of abscesses, and
- no increase in the number of draining fistulas from baseline.

The HiSCR will be derived from the individual lesion counts of abscesses, nodules and fistulae at scheduled visits as indicated in the assessments schedule and as such will not be recorded in the eCRF.

Individual lesion count

The HS affected areas e.g. right and left axillary (armpit), right and left gluteal ("buttock"), right and left inguinal-femoral (groin), perineal, pubic, sternal, right and left sub-mammary (breast) and others will be assessed by the physician for abscesses, inflammatory nodules, draining fistulas, total fistulas, and other lesions.

Whenever possible, the same physician should perform the lesion count throughout the study.

Inflammatory lesions, including abscesses, nodules, draining fistulae, total fistulae and other lesions will be counted by area.

Individual lesion counts will be performed for all lesions as outlined in the Table 8-1. The lesion count will include any existing and newly observed lesions and will be recorded in the eCRF. The HS lesions are defined as (Lipsker et al 2016; Zouboulis et al 2017):

- *Inflammatory nodules* (N) that are typically raised, deep-seated, three-dimensional, round, tender, erythematous, infiltrated and possibly pyogenic granuloma lesions with a diameter of >10 mm
- *Abscesses* (A) that are often inflammatory, painful, tender but fluctuating mass with a diameter of >10 mm, surrounded by an erythematous area; the middle of an abscess contains pus

[redacted]

- *Draining fistulae* (DF); sinus tracts, raised, tender but fluctuating longitudinal mass of variable length and depth, with communications to skin surface, draining purulent fluid
- *Fistulae* (F): total fistulae defined as sinus tracts, raised, tender but fluctuating longitudinal mass of variable length and depth, with communications to skin surface, both draining and non-draining purulent fluid.

8.3.2 Patient's Global Assessment of Skin Pain - NRS in the past 24 hours

The Patient's Global Assessment of Skin Pain - Numerical Rating Scale (NRS) in the past 24 hours will be used to assess pain "at its worst" and the average skin pain due to HS in the last 24 hours. The NRS is a segmented numeric version of the visual analog scale (VAS) in which a respondent selects a whole number (0–10 integers) that best reflects the intensity of their pain ranging from 0 (no skin pain) to 10 (skin pain as bad as you can imagine). Skin Pain will be collected as specified in the assessment schedule. To assess this, the patient should concentrate on the pain that his/her skin lesions generate. The Patient's Global Assessment of Skin Pain - NRS will be completed by the subject using the eDiary device.

8.3.3 Modified Hidradenitis Suppurativa Score (mHSS)

The Hidradenitis Suppurativa Score (Sartorius score) has been developed specifically for HS to reflect disease severity and has since been used as a modified score (mHSS) in clinical trials (Sartorius et al 2009; Kimball et al 2012) with minor simplifications when compared to the original score. The same seven anatomical areas as the HS-PGA are used. The following is recorded by the dermatologist:

- the anatomical regions involved: axilla, groin, gluteal (left/right) or other region, 3 points per region;
- the numbers and scores of lesions (inflammatory nodule or abcess - 1 point, draining fistula - 6 points) for each region;
- the longest distance between two relevant lesions (inflammatory nodule, abscess or draining fistula), or size of lesion if single, in each region: < 5 cm, 1 point; 5–10 cm, 3 points; > 10 cm, 9 points; and
- whether all lesions in each region are separated by normal skin: yes, 0; no (= Hurley III), 9 points.

Regional scores are added and summed up to the patient's total score. The upper limit of the scale is open. Results will be recorded in the eCRF.

Table 8-3 Modified Hidradenitis Suppurativa Score (mHSS)

Area evaluated	Number	Multiplier
Anatomical region involved: axilla, groin, gluteal (for all left/right location) or other region	Number of regions involved	x3 per each region
Number and severity of lesions		
Inflammatory nodules and abscesses	Number of inflammatory nodules and abscesses	x1 per each inflammatory nodule or abscess
Draining fistulas	Number of draining fistulas	x6 per each fistula

[redacted]

Area evaluated	Number	Multiplier
The longest distance between 2 relevant lesions or size of lesion (if single in each region).	Number of areas with the longest distance between 2 relevant lesions in each distance/size category	<5 cm: x1 5-10 cm: x3 > 10 cm: x9 no active lesions: x0
Are all lesions clearly separated by normal skin?	Number of areas in each category: with and without separation by normal skin	Yes: x0 No: x9
TOTAL SUM		

8.3.4 HS-Physician's Global Assessment (HS-PGA)

The HS-PGA score is a static global severity 6-point scale used and described by Kimball (Kimball et al 2012) (Table 8-4). It will be completed at scheduled visits as indicated in the Assessments schedule (Table 8-1). For a significant clinical response, at least a 2 point reduction is expected. The HS affected regions (e.g. right and left axillary, right and left gluteal (buttock), perianal, right and left inguinal-femoral (groin), others such as sub-mammary) are assessed for abscesses, draining fistulas, inflammatory nodules, and non-inflammatory nodules and one global rating / score is assigned to each patient. The scores will be recorded in eCRF.

Table 8-4 Hidradenitis Suppurativa Physician's Global Assessment Scale (HS-PGA)

Score	Rating	Description
0	Clear	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and 0 non-inflammatory nodules
1	Minimal	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and presence of non-inflammatory nodules
2	Mild	0 abscesses, 0 draining fistulas, and 1-4 inflammatory nodules or 1 abscess or draining fistula and 0 inflammatory nodules
3	Moderate	0 abscesses, 0 draining fistulas, and ≥5 inflammatory nodules or 1 abscess or draining fistula and ≥1 inflammatory nodules or 2-5 abscesses or draining fistulas and <10 inflammatory nodules
4	Severe	2-5 abscesses or draining fistulas and ≥10 inflammatory nodules
5	Very severe	>5 abscesses or draining fistulas

8.3.5 Dermatology life quality index (DLQI)

The Dermatology Life Quality Index (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

[redacted]

30, with higher scores indicating greater HRQoL impairment. Each subscale of the DLQI may also be analyzed separately. DLQI will be completed by the subject using the eDiary device.

8.3.6 Health Status Questionnaire (EQ-5D-3L)

The EQ-5D-3L is a generic instrument used to assess subject's health status. The recall period is "today", and the instrument takes 1 to 2 minutes to complete. The instrument consists of two pages – the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three response levels: no problems, some problems, severe problems. The subject is asked to indicate the subject's health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the five dimensions. The VAS records the respondent's self-rated health on a vertical 20-cm visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'. EQ-5D-3L will be completed by the subject using the eDiary device.

8.3.7 Hidradenitis Suppurativa Symptom Diary

Novartis is currently developing a novel diary of HS symptoms and impact of HS on patient's life self-reported by the subject: The HS Symptom Diary. The HS Symptom Diary will be available in a limited number of languages and will be available on eDiary devices. If the HS Symptom Diary is available in the country in which a study site is located, the subjects must participate in the diary assessments.

The site staff must train the subject on the use of the eDiary prior to dispensing the diary device during the screening period (e.g., at the Screening Visit [Screening 1]). The diary device may be dispensed to the subject -4 weeks to -1 week prior to randomization. For example, if the device was not available for the subject at Screening Visit 1 due to resource supply at the site, the site may dispense the device to the subject later in the screening period.

[redacted]

The HS symptom diary is being developed in accordance with the FDA's 2009 Guidance for Industry, Patient Reported Outcomes: Uses in Medical Product Development to Support Labeling Claims.

[redacted]

Subject eDiary training

At the initial study visit (Screening Visit 1), subjects will complete the initial eDiary training during which they will learn to use the eDiary's protocol-specific and general features.

Subject and site training materials will be provided to the subjects and to the study sites.

8.3.8 Patient Global Impression of severity (PGI-s)

Patient Global Impression of severity (PGI-s) rates the severity of the current HS on a scale ranging from "none" to "very severe". The PGI-s is self-administered and is to be completed as per the assessment schedule on the electronic tablet at the investigational site. The PGI-s is based on the validated Clinical Global Impression of severity scale.

8.3.9 Patient Global Impression of Change (PGI-c)

The Patient Global Impression of change (PGI-c) is a patient-reported instrument that measures change in overall status on a scale ranging from one ("very much improved") to seven ("very much worse"). PGI-c rates the current HS symptoms as compared to the start of the study at visits indicated in the assessment schedule. The PGI-c is self-administered and is to be completed as per the assessment schedule on the electronic tablet at the investigational site. The PGI-c is based on the validated Clinical Global Impression of change scale.

8.3.10 Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP)

The WPAI-SHP consists of six questions regarding current employment status, hours missed from routine work due to a disease/other reasons, the number of hours actually worked, and the degree to which HS affected productivity/regular activities over the past seven days. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e. worse outcomes.

8.3.11 Patient's lesion count

This is a self-reported patient's assessed count of existing and new lesions in the HS affected areas. The Patient's lesion count will be implemented on the eDiary and will be assessed on a weekly basis.

8.3.12 Appropriateness of efficacy assessments

The primary and secondary endpoints reflect the most important domains in HS as proposed by the scientific community (Thorlacius et al 2018). The primary endpoint used in this study, HiSCR, was developed and validated as part of the development program of adalimumab in HS. The HiSCR is considered to be adequately described and validated for its intended purpose as the primary end-point in pivotal studies (Humira (adalimumab) EPAR).

The secondary endpoint definition of flare is based on physician lesion counts and has been previously used in clinical trials in HS. The secondary endpoint of efficacy assessment used for evaluation of pain relief (NRS) is standard recommended primary outcome measures for pain clinical trials, also supported by Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines. As chronic pain interferes with daily activities and quality of life,

[redacted]

additional patient reported outcome measures (PROs) of physical functioning and health-related quality of life (HRQoL) tools are recommended for assessing the patient's perception of the impact of disease and treatment on daily life, physical, psychological and social functioning, and well-being. Therefore, DLQI, EQ-5D, PGI-s, PGI-c and WPAI are included as exploratory endpoints. These PROs are not disease specific, but applied conventionally in other chronic diseases. The HS-specific exploratory endpoints of HS-PGA and mHSS have been used in previous HS trials.

8.4 Safety

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

In case of a global health event (e.g. pandemic, epidemic) that limits or prevents on-site study visits, regular phone contacts or virtual calls, depending on feasibility and technical requirements, will occur (approximately every 4 weeks, prior to home administration, or more frequently if needed) for safety monitoring and discussion of the subject´s health status until the subject can again visit the site. Events qualifying for being reported in the case report form (e.g. AE, infection) should be entered as appropriate.

If subjects cannot visit the site to have blood/urine samples drawn for central lab analysis, investigator may consider performing the safety lab tests locally, e.g. by the patient´s general practitioner, in case it is needed to check safety parameters.

If female subjects of child bearing potential cannot visit the site to have urine pregnancy tests done, urine pregnancy test kits may be shipped or provided directly to the subject (e.g. together with the study drug). After appropriate instruction, subjects should perform the urine pregnancy test at home and report the result to the site. It is important that subjects do the pregnancy test first and only if the test result is negative proceed with the administration of the study drug. A communication process should be established with the subject so that the site is informed of the pregnancy test results.

Alternatively, depending on local regulations and capabilities, study site staff may visit the subject at home to draw blood/ urine samples if needed. Sites should inform the Sponsor of proposed changes to sample management/ collection.

8.4.1 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. Significant findings that are present prior to the start of study treatment must be

included in the Medical History eCRF. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event eCRF.

8.4.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed at every scheduled visit 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, heart rate, systolic and diastolic **blood pressure will be measured twice** (measurements separated by 1 to 2 minutes) using a validated device, with an appropriately sized cuff. 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.

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.

8.4.3 Height and weight

Height and body weight will be measured as indicated in Table 8-1.

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg)) will be measured in indoor clothing, but without shoes. If possible, body weight assessments should be performed by the same study site staff member and using the same scale throughout the study. The body weight recorded at the Randomization visit will be used to stratify the subject population for randomization.

8.4.4 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.

Blood withdrawals and safety assessments should be done prior to study treatment administration and should be taken as shown in Table 8-1 and in Table 16-1.

Section 16.1 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.

8.4.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count will be measured at all scheduled study visits as specified in Table 8-1.

8.4.4.1.1 Erythrocyte sedimentation rate (ESR)

The ESR test will be performed locally by unblinded person using the ESR Supplies kit provided by the central laboratory. A laboratory manual will be provided with detailed information on sample collection and handling. In order to preserve the blind, results of ESR will not be communicated to the other study site staff, including the investigator, or to Novartis during the study.

8.4.4.2 Clinical chemistry

Serum chemistry will include urea, creatinine, HbA1c, total bilirubin, AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, lipase, amylase, and uric acid. Serum chemistry will be measured at all scheduled study visits as specified in Table 8-1.

8.4.4.2.1 Lipid panel

A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), total cholesterol and triglycerides will be measured from a fasting blood sample as indicated in Table 8-1.

8.4.4.2.2 High sensitivity C-reactive protein

High sensitivity C-reactive protein (hsCRP) will be assessed centrally as part of the clinical chemistry panel as indicated in Table 8-1. In order to preserve the blind, results of hsCRP will not be communicated to the study site staff, including the investigator, or to Novartis during the study.

8.4.4.3 Local urinalysis

Dipsticks will be provided by the central laboratory to the study sites for local urinalysis assessments. Standard dipstick measurements for specific gravity, protein, glucose, pH, blood, urine blood dipstick (non-hemolyzed), urine blood dipstick (hemolyzed), bilirubin, ketones and WBC will be done at scheduled visits as indicated in Table 8-1. If the standard dipstick result is positive, microscopy assessments will be performed and recorded in the source data.

8.4.4.4 Immunogenicity

Blood samples for immunogenicity (IG, anti-secukinumab antibodies) will be taken pre-dose at the scheduled time points as indicated in Table 8-1. All blood samples (approximately 2 mL each) will be taken by direct venipuncture.

The blood sample will be allowed to clot at room temperature prior to harvesting of the serum. The serum will be obtained by centrifugation, split into 2 aliquots and then stored at approximately -70˚C to -20˚C prior to shipment on dry ice to the central laboratory.

[redacted]

For a detailed description of the blood sampling schema, including time points, refer to the Blood Log in Section 16.2, Table 16-1.

A laboratory manual will be provided by the central laboratory with detailed information on sample collection, sample handling and shipment.

The actual sample collection date and exact time of collection will be entered on the eCRF capturing blood collection for IG. Sampling problems will be noted in the 'Reason sample not taken' section of the eCRF. In case unscheduled IG samples are taken, there should always be matching PK samples taken as well.

Immunogenicity analytical method

An electrochemiluminescence-based method will be used for the detection of potential anti-secukinumab antibody formation. A detailed description of the method to assess immunogenicity will be described in the bioanalytical raw data and in the respective Bioanalytical Data Report (BDR).

8.4.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Pregnancy tests will be performed in all women of childbearing potential (see Section 5.2 for definition of childbearing potential), as indicated in Table 8-1.

Any woman with a confirmed positive pregnancy test during screening is not eligible for randomization. A positive local urine pregnancy test during the treatment periods of the study requires immediate interruption of study treatment until a serum β-subunit of human chorionic gonadotropin (β-hCG) test is performed and found to be negative. If the serum β-hCG test is positive, the subject must be discontinued from the study treatment.

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or bilateral tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of childbearing potential must also be available as source documentation in the following cases:

1. surgical bilateral oophorectomy without a hysterectomy
2. reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female subject, regardless of reported reproductive/menopausal status at screening/baseline.

8.4.6 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic immunomodulating agent in HS.

[redacted]

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

The impact of HS on various aspects of subject's health-related quality of life (HRQoL) will be assessed by the following and are described in Section 8.3:

- Patient Global Assessment of Skin Pain (NRS)
- Dermatology Life Quality Index (DLQI)
- EuroQoL 9 Dimension Health Questionnaire - Health Status Questionnaire (EQ-5D-3L)
- Patient Global Impression of severity (PGI-s)
- Patient Global Impression of change (PGI-c)
- Work Productivity Activity Impairment (WPAI)
- HS Symptom Diary

All these questionnaires (except for questionnaires completed by subjects on the eDiary at home including Patient's Global Assessment of Pain NRS and HS Symptom Diary) should be completed by subjects **before** any study related clinical assessments by the investigator take place. Responses to HRQoLs will be collected as per the eCOA manual on eDiary or site pad.

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. Before the investigator begins the clinical assessments, the study coordinator should check the questionnaires for completeness and encourage the subject to complete any missing responses.

After the investigator completes the clinical efficacy assessments (e.g. lesion count), the investigator will review and the examine questionnaires completed by the subject for responses that may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the subject. If AEs or SAEs are confirmed then the investigator must record the events as per instructions given in Section 10 of the protocol. The investigator/site staff should not encourage the subject to change the responses reported in the completed questionnaires.

8.5.2 Pharmacokinetics

Details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual.

At all study sites, blood samples will be collected pre-dose for PK analysis at the scheduled visits as indicated in Table 8-1.

For a detailed description of the blood sampling schema, including time points, refer to the Blood Collection Log in Table 16-1.

Blood samples (approximately 2 ml, not less than 1.5 ml) will be collected into Serum Separator Tubes (SST). All blood samples will be taken by direct venipuncture. The blood sample will be allowed to clot over a minimum of 30 minutes at room temperature prior to harvesting of the serum. The serum will be obtained by centrifugation at approx. 2500 Revolutions Per Minutes (RPM) for 10 minutes. Thereafter, the serum samples will be placed on ice, split into 2 aliquots

[redacted]

(labelled plain barrier polypropylene tubes) and then stored (within 30 minutes of serum collection by centrifugation) at -70˚C to -20˚C. The shipment to the central laboratory should be made on dry ice. The shipment instructions will be provided by the central laboratory. If possible, each aliquot of a sample should be sent separately to the central laboratory. The back-up samples should remain at the central laboratory whereas the second batch (the second pair) is delivered to an analytical laboratory. Back-up samples at the Central Laboratory will only be disposed after approval by the corresponding Study Leader (typically six to 12 months after the clinical study report (CSR) is published).

The actual sample collection date and exact time of collection should be entered in the Blood Collection for PK eCRF or in the Unscheduled Blood Collection for PK eCRF, as appropriate. Sampling problems should be noted in the 'Reason sample not taken' section of the eCRF.

PK sample handling, labeling and shipment instructions

A laboratory manual will be provided by the central laboratory with detailed information about sample collection, handling and shipment.

Tubes and labels will be provided by the central laboratory with study/sample type and sample number pre-printed on the label.

Further details on labeling of the pharmacokinetics samples can be found in Table 16-1.

PK sample stability

Secukinumab is stable in serum samples for 4 months at -20°C or at -80°C. Long-term data confirmed a stability of 39 months at -65°C to -90°C.

PK analytical methods

An ELISA method will be used for the bioanalytical analysis of secukinumab in serum, with an anticipated lower limit of quantification (LLOQ) of 80 ng/ml. The detailed method description to assess secukinumab concentration will be described in the Bioanalytical Data Report (BDR).

8.5.3 Biomarkers

8.5.3.1 Additional biomarker assessments

8.5.3.1.1 Exploratory serum biomarkers

Serum samples will be collected for exploratory biomarkers.

Apart from hsCRP, as a general indicator of inflammation, no biomarkers are available which are validated and accepted to assess disease stage, severity, efficacy of treatments or stratification of HS patients for targeted treatments. Therefore, serum samples will be collected for exploratory biomarker assessments.

[redacted]

[redacted]

These exploratory samples will be biobanked and analyzed depending on results of the overall study outcome, other biomarker assessments in this study, and/or results from other studies and/or based on literature, new published results, or new internal results. The samples may be analyzed to support additional research to identify new HS therapies and to further understand HS pathobiology and that of other related diseases.

Further details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual.

8.5.3.1.2 Optional biopsy sampling substudy

The study includes an optional biopsy substudy which requires a separate informed consent signature if the patient agrees to participate. Only patients from sites with interest in the optional biopsy substudy will be invited to participate. Sites and patients are encouraged to participate in the study, given the importance of the related research and the need to reflect the variability of HS pathobiology.

Formalin-fixed paraffin-embedded (FFPE) lesion punch biopsy samples from baseline and on-treatment will be sent to the central laboratory. Detailed instructions on sample harvesting, preparation and storage will be provided in the Laboratory Manual.

Exploratory biopsy research will entail histology and transcriptomic. The intermediate products of gene expression, such as mRNA, will be used to examine gene expression signatures using suitable gene expression profiling techniques including next generation sequencing. This substudy may include, but is not limited to, analyses to gain a better understanding of the mechanistic aspects of HS. These data may also support the identification of pathways/markers that characterize the disease or response to treatment with secukinumab.

8.5.3.1.3 Optional DNA sampling

The study includes an optional DNA component which requires a separate informed consent signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents these options to the patient.

Exploratory DNA research studies are planned as a part of this study with the objectives of identifying genetic factors which may (1) predict response to treatment with secukinumab; (2) predict relative susceptibility to drug-drug interactions; (3) predict genetic predisposition to side effects; or (4) be related to HS or autoimmune diseases.

With the advances in technology over time, the most appropriate technology will be used at the time the exploratory DNA research is performed. This may include the study of the entire genome (whole genome sequencing).

[redacted]

Laboratory Manual will contain detailed information on sample collection, handling, and shipment.

8.5.4 Other Assessments

8.5.4.1 Trial feedback questionnaire

This trial will include an option for subjects to complete an anonymized questionnaire, referred to as a 'Trial Feedback Questionnaire'. This questionnaire will give subjects an opportunity to provide feedback on their clinical trial experience. Individual subject level responses will not be reviewed by investigators. Responses will be used by the sponsor (Novartis) to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the subject's disease, symptoms, treatment effect or adverse events, and therefore is not considered trial data. Should any spontaneous information be collected about AEs, this will be transferred to the safety database.

8.5.4.2 Health Care Resource Utilization

Studies conducted in Canada and the United States have indicated the high economic impact of the disease both on a direct level (due to hospitalizations and emergency department visits) and on an indirect level (occupational disability). All-cause and HS-related outpatient visits, inpatient stays and emergency visits not planned per protocol will be collected to explore possible decreases in utilization of these resources. Health Care Resource Utilization will be entered on eCRF.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

Subjects may voluntarily discontinue study treatment for any reason at any time.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject's wish
- Withdrawal of consent
- Pregnancy
- Ongoing use of prohibited treatment as per the prohibited treatment Section 6.2.2
- Any situation in which study participation might result in a safety risk to the subject
- Following emergency unblinding

[redacted]

- Emergence of the following adverse events: any adverse events that in the judgment of the investigator/qualified site staff, taking into account the subject's overall status, prevent the subject from continuing study treatment (for example, sepsis)
- Any laboratory abnormalities that in the judgment of the investigator/qualified site staff, taking into consideration the subject's overall status, prevents the subject from continuing study treatment

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information in the eCRF.

Subjects who discontinue study treatment should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Withdrawal of Informed Consent, Section 9.1.2). **Where possible, they should continue attending site visits for the assessments indicated** in the assessment schedule (including efficacy assessments). If the subject does not wish to attend any further visits, the subject should return to the site after discontinuation of study drug, for an End of Treatment (EOT) visit and Follow-up visit (F8). Assessments detailed in the EOT and Follow-up visit (F8) in Table 8-1 should be completed and recorded in the eCRF. If the subject fails to return for these 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 (Section 9.1.3). This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), 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.

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 Emergency breaking of treatment code section.

9.1.2 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

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- 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.

[redacted]

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 retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 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.

9.1.4 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 instructions on when the subject should stop self-administration of study drug and 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 Institutional Review Board/Independent Ethics Committee (IRB/IEC) 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, 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 when she/he has completed the last visit planned in the protocol (visit at Week 52 or visit at Week 60 (F8)). The Study Completion visit for individual patient will be defined as:

- Week 60 (F8) visit for subjects who prematurely discontinue study treatment in Treatment Periods 1 or 2 for any reason, or subjects who complete treatment period but do not enroll in the planned extension study
- Week 52 visit for subjects continuing in the planned extension study

[redacted]

At the end of the study, patients who completed the core study treatment period are expected to benefit from study treatment based on the investigator's clinical judgement, and wish to participate will be eligible to continue into a planned extension study. The extension study is intended to collect further safety and efficacy data on secukinumab, provide continuous access to treatment for patients and evaluate the sustainability of the treatment effect after study drug discontinuation (in the randomized withdrawal part of this study).

The investigator must provide follow-up medical care for all subjects who are pre-maturely withdrawn from the study or do not continue in the extension study, or must refer them for appropriate ongoing care. This care may include use of long term antibiotics, surgical intervention and/or use of biologics.

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 if 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

[redacted]

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 study drug, the interventions required to treat it, and the outcome.

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

[redacted]

baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

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.

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.

[redacted]

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 10 weeks following the last administration of study treatment 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. Any SAEs reported up to the subject's last visit will be reported in the AE eCRF. SAEs beyond that date will only be recorded in the Safety database.

10.1.4 Pregnancy reporting

If a female subject becomes pregnant, the study treatment should be stopped, and the subject must be asked to read and sign a pregnancy consent form to allow the Study Doctor to ask questions about her 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.

[redacted]

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 (European Medicines Agency 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 collected in the DAR (dose administration record) eCRF 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 Dose Administration (DAR) eCRF (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.

10.2.1 Data Monitoring Committee

This study will include a Data Monitoring Committee (DMC) that will function independently of all other individuals associated with the conduct of the clinical trial, including the site investigators participating in the study. The DMC will assess [redacted] the progress of a clinical trial, safety data, and critical efficacy variables, and it will recommend to the sponsor whether to continue, modify or terminate a trial.

Specific details regarding the composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.2.2 Steering Committee

A Steering Committee (SC) will be established comprising disease area experts, investigators participating in the trial, i.e. not being members of the DMC and Novartis representatives from the CTT.

[redacted]

The SC will ensure transparent management of the study according to the protocol by recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC 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

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

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (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 (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.

11.2 Database management and quality control

Novartis personnel (or designated contract research organization (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

[redacted]

will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) 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.

DNA samples:

To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the subject's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the subject's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

The use of DNA to search for biomarkers of disease and drug action is exploratory. Any results from this DNA study will not be placed in the subject's medical records.

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. 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 eCRFs 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 eCRFs are performed according to the

[redacted]

study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

In the event of a major health care disruption (e.g. pandemic, epidemic), requiring social distancing or limited travel/attendance to site, remote site initiation and monitoring could be considered.

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 to 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 patient took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

For all analysis in Treatment Period 1, the Placebo group to secukinumab 300 mg every 2 weeks and Placebo group to secukinumab 300 mg every 4 weeks will be pooled together.

12.2 Subject demographics and other baseline characteristics

The analysis of subject demographics and other baseline characteristics data will be based on Randomized Analysis Set.

Demographics and baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristic variables for each treatment group and for all subjects. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and for all subjects.

Medical history

Any condition entered as medical history or current medical conditions at baseline will be coded using the MedDRA dictionary. Medical history will be summarized by system organ class and preferred term in the MedDRA dictionary.

[redacted]

12.3 Treatments

The analysis of study treatment data will be based on the Safety Set.

The number of active and placebo injections will be summarized by treatment group by means of contingency tables.

The duration of exposure to study treatment will also be summarized by treatment group. In addition, the number of subjects with exposure of at least certain thresholds (e.g., any exposure, ≥1 week, ≥2 weeks, ≥3 weeks, ≥4 weeks, ≥8 weeks, etc.) will be displayed.

Prior and concomitant treatments

Prior and concomitant treatments will be summarized by treatment group in separate tables for the Safety Set.

Prior treatments are defined as treatments taken and stopped prior to first dose of study treatment. Any treatment given at least once between the day of first dose of randomized study treatment and the last day of study visit will be a concomitant treatment, including those that were started pre-baseline and continued into the treatment period.

Treatments will be presented in alphabetical order, by ATC codes and main groups. Tables will also show the overall number and percentage of subjects receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

In addition, medical procedures and significant non-drug therapies as coded in MedDRA will be summarized.

12.4 Analysis of the primary endpoint(s)

The primary aim of the study is to demonstrate the efficacy of two secukinumab regimens compared to placebo with respect to HiSCR after 16 weeks of treatment. The detailed definition and the justification of the corresponding primary Estimand, as well as the definition of the supplementary Estimands will be provided in the Statistical Analysis Plan.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is HiSCR at Week 16, defined as at least a 50% decrease in Abscess and inflammatory Nodule (AN) count compared to baseline with no increase in the number of abscesses and/or in the number of draining fistulas from baseline to Week 16. The baseline is defined as the last assessment (including unscheduled visits) obtained before/on the day of the first administration of the study treatment, or on the randomization date if there has been no drug administration.

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

12.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypotheses for the primary endpoint being tested is that there is no difference in the proportion of HiSCR at Week 16 in any of the secukinumab regimens versus placebo regimen.

Let p_j denote the proportion of HiSCR at Week 16 for treatment regimens j, j = 0, 1, 2 where

[redacted]

- 0 corresponds to placebo regimen,
- 1 corresponds to secukinumab 300 mg q2w s.c.,
- 2 corresponds to secukinumab 300 mg q4w s.c.,

In statistical terms, Hj: $p_j = p_0$, $H_{Aj} : p_j \neq p_0$ for the jth secukinumab regimen, i.e.

H1: secukinumab 300 mg q2w s.c. is not different to placebo regimen with respect to HiSCR after 16 weeks of treatment.

H2: secukinumab 300 mg q4w s.c. is not different to placebo regimen with respect to HiSCR after 16 weeks of treatment.

The primary analysis method will be logistic regression with treatment group, geographical region, Hurley stage, use of antibiotic, baseline body weight and baseline AN counts as explanatory variables. Odds ratios will be computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted. In case of response rates of 0% or of 100% in one of the treatment groups, Fisher's exact test will be applied. Risk difference and confidence intervals for risk difference will be provided.

The detailed testing strategy including the primary endpoint analysis is provided in Section 12.5. Efficacy of two secukinumab regimens compared to placebo with respect to HiSCR after 16 weeks of treatment could be demonstrated if H1 and/or H2 is/are rejected and the treatment effect is in favor of secukinumab.

12.4.3 Handling of missing values/censoring/discontinuations

Missing data for primary and secondary endpoints will be addressed using multiple imputation.

As these endpoints are binary outcomes derived from underlying continuous variables, the imputations will be performed on those continuous variables, from which the imputed binary outcomes will then be constructed. Subjects who discontinue from study treatment early will be encouraged to stay in the study and are considered as retrieved dropout (RDO) subjects. The analysis will account for different post-randomization events for missing data handling as follows:

Permanent discontinuation of study treatment due to AE (Adverse Event), LoE (Lack of Efficacy): If retrieved dropout data are available, these will be used for analysis. If no data was retrieved after study treatment discontinuation, missing data will be multiply imputed based on placebo arm data (Carpenter et al 2013). More details on the imputation model will be specified in the Statistical Analysis Plan prior to unblinding.

Permanent discontinuation of study treatment due to other reasons than AE (Adverse Event), LoE (Lack of Efficacy): If efficacy data collected after study treatment discontinuation are available (retrieved dropout), then the retrieved drop-out data will be excluded and missing data after study treatment discontinuation will be multiply imputed using the MAR (missing at random) assumption. In case of a major health event (e.g. pandemic/epidemic), the number of missing measurements may increase and the potential to recover information for the main endpoints from intermediate measurements that have been dropped from the visit schedule may decrease. This may affect the power of tests and the precision of estimates for this study.

[redacted]

Furthermore, the Sponsor might consider additional analyses to assess any potential impact of a major health event on our study results. Detailed information, including missing data handling plan and additional analysis will be specified in the Statistical Analysis Plan.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

To further support the primary estimand, sensitivity analyses will be considered in the way of varying assumptions about the missing outcomes between treatment arms.

Another sensitivity analysis will be performed where the baseline is defined as weighted average of first screening visit (with weight 1/6) and the second screening visit (with weight 2/6) and the randomization visit (with weight 3/6). This weighted average is being used during the study to identify the need for rescue medication and it is also used at Week 52 to identify responders being randomized in the extension study.

Supportive analyses

A supplementary estimand, which is detailed in the Statistical Analysis Plan, and following analyses will also be done to support primary endpoints:

- The number and percentage of subjects will be presented for proportions of subjects who achieved at least 50%, 75% and 100% reductions in the AN count relative to Baseline (AN50, AN75, AN100).
- Summary statistics will be presented for absolute and percent change from Baseline in AN count.
- Summary statistics will be presented for absolute and percent change from Baseline in number of abscesses.
- Summary statistics will be presented for absolute and percent change from Baseline in number of inflammatory nodules.
- Summary statistics will be presented for absolute and percent change from Baseline in number of draining fistulas.

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:

- Percentage change from baseline in AN count at Week 16
- Flare over 16 weeks: Patients who experience at least one flare over 16 weeks. Flare is defined as an at least a 25% increase in AN counts with a minimum increase of 2 AN relative to baseline.
- Pain/NSR30 at Week 16: Patients achieving NRS30 at Week 16, among patients with baseline NRS $\geq$ 3. NRS30 is defined as at least 30% reduction and at least 2 unit reduction from baseline in Patient's Global Assessment of Skin Pain. NRS from baseline to Week 16 is the weekly average score calculated based on the 7 available daily scores: Baseline (Week 0) will be average of NRS score from day -7 to day -1, week 1 will be average of

[redacted]

score from day 1 to day 7, week 2 will be average of score from day 8 to day 14 and so on. For any week with less than 4 diary entries within the week, the weekly average will be recorded as missing.

For the secondary endpoint of percentage change in AN count from baseline to Week 16, an analysis of covariance (ANCOVA) model will be fitted to estimate the treatment differences between the two secukinumab regimens and placebo with treatment group, baseline AN count, Hurley stage, use of antibiotic, geographical region and baseline body weight as covariates.

The analysis method for both flare up to Week 16 and Pain/NRS30 at Week 16 will be the logistic regression: with treatment group, Hurley stage, geographical region, use of antibiotic, baseline body weight and baseline AN counts as explanatory variables for flare endpoints; and with treatment group, Hurley stage, region, use of antibiotic, baseline body weight and baseline NRS as explanatory variables for pain endpoints. Odds ratios will be computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted. In case of response rates of 0% or of 100% in one of the treatment groups, Fisher's exact test will be applied. Risk difference and confidence intervals for risk difference will be provided.

Testing strategy

Two studies of identical design (CAIN457M2301 and CAIN457M2302) are planned, each with multiple endpoints. Primary endpoint, secondary endpoints percentage change from baseline in AN count at Week16 and flare over 16 weeks will be tested in each of the two studies separately. Pain/NSR30 at Week 16 will be tested using the combined data from the two studies. In order to control for the type-I error rate ("false positive rate") at the level of the individual studies, and at the level of the combined dataset of both studies, the testing strategy illustrated in Figure 12-1 below will be implemented.

The hypotheses included in the test procedure are listed below:

Primary endpoint (as described in Section 12.4):

H1(H'1): secukinumab 300 mg q2w s.c. is not different to placebo regimen with respect to HiSCR after 16 weeks of treatment.

H2(H'2): secukinumab 300 mg q4w s.c. is not different to placebo regimen with respect to HiSCR after 16 weeks of treatment.

Secondary endpoints:

H3(H'3): secukinumab 300 mg q2w s.c. is not different to placebo regimen with respect to percentage change from baseline in AN count at Week 16

H4(H'4): secukinumab 300 mg q4w s.c. is not different to placebo regimen with respect to percentage change from baseline in AN count at Week 16

H5(H'5): secukinumab 300 mg q2w s.c. is not different to placebo regimen with respect to flare over 16 weeks of treatment

H6(H'6): secukinumab 300 mg q4w s.c. is not different to placebo regimen with respect to flare over 16 weeks of treatment

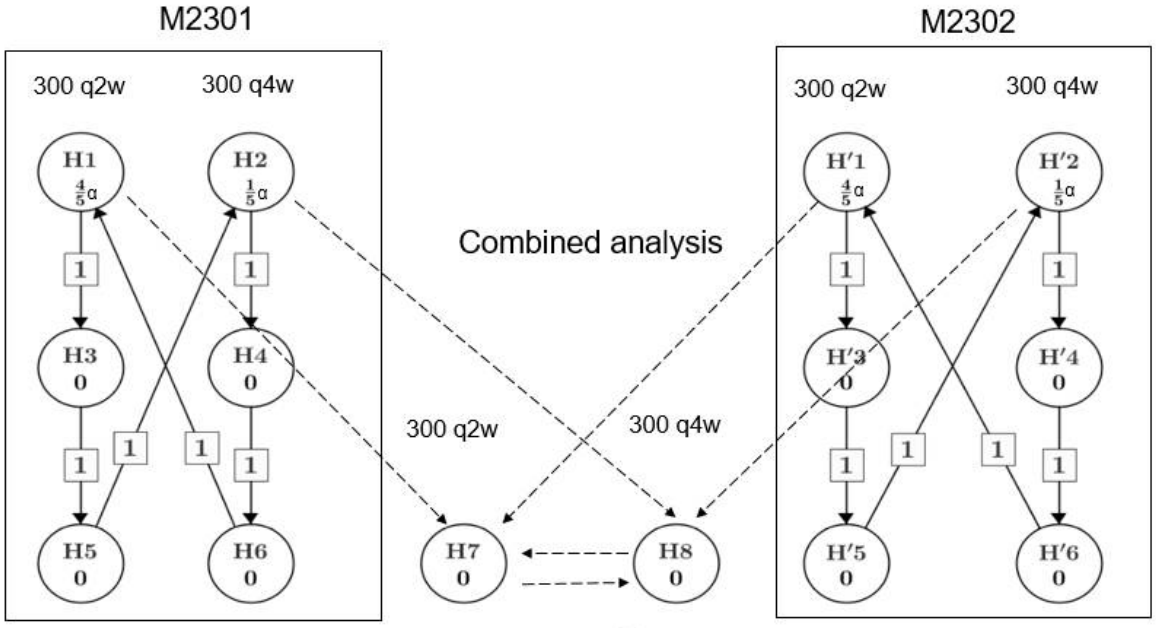
H7: secukinumab 300 mg q2w s.c. is not different to placebo regimen with respect to NRS30 at Week 16

[redacted]

H8: secukinumab 300 mg q4w s.c. is not different to placebo regimen with respect to NRS30 at Week 16

Efficacy of two secukinumab regimens compared to placebo with respect to percentage change from baseline in AN count at Week 16 could be demonstrated if H3(H'3) and/or H4(H'4) is/are rejected and the treatment effect is in favor of Secukinumab. Efficacy of two secukinumab regimens compared to placebo with respect to flare over 16 weeks could be demonstrated if H5(H'5) and/or H6(H'6) is/are rejected and the treatment effect is in favor of secukinumab. Efficacy of two secukinumab regimens compared to placebo with respect to Pain/NSR30 at Week 16 could be demonstrated if H7 and/or H8 is/are rejected and the treatment effect is in favor of secukinumab.

Figure 12-1 Testing strategy



Testing procedure and type-I-error control in the planned submission includes studies CAIN457M2301 and CAIN457M2302 (both with identical design). Hypotheses can only be tested in the order as indicated by the arrows. The hypothesis H1 of the primary objective (HiSCR at Week 16) for the high dose secukinumab regimen (q2w) versus placebo will be tested at 4α/5 while the hypothesis H2 of the primary objective (HiSCR at Week 16) for the low dose secukinumab regimen (q4w) versus placebo will be tested at α/5 simultaneously. If at least one of H1 and/or H2 are/is rejected then H3 and/or H4 (percentage change from baseline in AN count at Week 16), is tested. If at least one of H3 and/or H4 are/is rejected, then the corresponding alpha will be passed to H5 and/or H6 (flare over 16 weeks) respectively. Once HiSCR, percentage change in AN count and flare hypotheses for a secukinumab regimen are rejected, the respective 4α/5 for the high dose and α/5 for the low dose can be passed on to the other regimen's hypotheses, if they are not already rejected at the initial significance level (i.e., α/5 for the low dose and 4α/5 for the high dose). If both studies independently reject the primary null-hypothesis on the same secukinumab regimen (H1 and H'1, or H2 and H'2), then the corresponding secukinumab regimen's pain hypothesis (H7 or H8) can be tested. Additionally,

[redacted]

the significance level for the pain hypothesis can be passed from one dose regimen to the other dose regimen if one pain dose regimen is rejected and the primary null-hypothesis on the two secukinumab regimen are all rejected. The initial significance level for pain hypothesis (H7 and/or H8) is set to α-α^2. The subtraction of α^2 is to account for the maximum possible type I error to claim a success for HiSCR, percentage change in AN count and flare in both studies. Therefore, the type I error rate is controlled at level α for the submission on all hypothesis endpoints. The detailed information regarding the significance level of H7 and H8 can be found in Section 16.3 (Appendix 3: Type I alpha for the pain hypothesis). Under the global null hypothesis (i.e. no difference between secukinumab and placebo), the testing procedure outlined above controls the type I error rate (one-sided) at the study-level to <0.025, and at the submission level to <0.000625(=0.025^2). Considering all possible configurations of true and false null hypotheses, the type I error control at the level of the submission is <0.000625 for the primary objectives, and <0.025 for all hypotheses (Bretz et al 2019).

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 last dose, or events present prior to the first dose of study treatment but increased in severity based on preferred term within 84 days after last dose) 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.

Confidence intervals for relative frequencies will be derived as well according to the score method including continuity correction by Newcombe (Newcombe 1998).

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

A graphical display of relative frequencies within system organ classes will be presented.

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.

[redacted]

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.

For each parameter, the maximum change from baseline within each study treatment period will be analyzed analogously.

In addition, shift tables will be provided for all parameters based on Common Toxicity grade Criteria (CTC). For these shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high relative to the baseline value. These summaries will be presented by laboratory test and treatment group. Shifts will be presented for most extreme values post-baseline.

Immunogenicity

All immunogenicity results will be listed by treatment group, subject and visit/time.

Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation and will be carried out and reported as a separate activity.

12.5.3 Pharmacokinetics

PK concentrations will be listed by treatment and subject and Cmin will be determined. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum.

12.5.4 DNA

Exploratory DNA studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests are used for the analyses. Additional data, from other clinical trials, are often needed to confirm associations. Alternatively, if the number of subjects enrolled in the study is too small to complete proper statistical analyses, the data may be combined, as appropriate, with those from other studies to enlarge the dataset for analysis.

[redacted]

12.5.5 Biomarkers

All biomarker data will be listed by treatment group, subject and visit. Summary statistics will be provided by treatment and visit. The number of values outside of the limits of quantification will be reported in each table.

Exploratory biomarker assessments will be reported separately.

[redacted]

12.5.6 PK/PD relationships

The effect of the secukinumab serum concentration on HiSCR and other endpoints will be investigated if appropriate. Clinically important subject covariates, such as Hurley stage, geographical region, use of antibiotic, baseline body weight, age and baseline AN count will be investigated.

12.5.7 Patient reported outcomes

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

12.6 Analysis of exploratory endpoints

For the exploratory endpoints analyses, the estimates of the differences between secukinumab groups versus placebo group and the corresponding p-values for pairwise comparisons will not be adjusted for multiple comparisons as no formal confirmatory hypothesis tests are planned.

Subpopulation Analysis

The number and percentage of HiSCR responders in bio-naive patients will be presented by visit up to end of study for each treatment group.

The number and percentage of HiSCR responders in patients with body weight lower and higher than 90kg (<90kg and ≥90kg) will be presented by visit up to the end of study for each treatment group.

To allow for a pairwise comparison between the two secukinumab regimens and placebo at Week 16 in bio-naive patients, HiSCR at Week 16 will also be analyzed in bio-naive patients using logistic regression with treatment group, geographical region, Hurley stage, baseline AN count use of antibiotic, and baseline body weight as explanatory variables. Odds ratios will be computed for the comparison of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted. In case of response rates of 0% or of 100% in one of the treatment groups, Fisher's exact test will be applied. Risk difference and confidence intervals for risk difference will be provided.

The subgroup analysis of patients with bodyweight lower and higher than 90 kg (<90kg and ≥90kg) will be analyzed analogously to bio-naive patients.

Modified Hidradenitis Suppurativa Score

Summary statistics will be provided for absolute and percent change from baseline of modified Hidradenitis Suppurativa Score by visit up to end of study.

To allow for a pairwise comparison between two secukinumab regimens and placebo until Week 16, modified Hidradenitis Suppurativa Score up to Week 16 will also be analyzed using a MMRM with treatment group, the respective baseline value, Hurley stage, use of antibiotic, geographical region, baseline bodyweight, visit, baseline mHSS*visit interaction, and treatment group*visit as covariates, with unstructured covariance matrix.

[redacted]

HS-Physician's Global Assessment

HS-PGA responder will be analyzed using logistic regression with treatment group, Hurley stage, geographical region, use of antibiotic, baseline bodyweight, baseline HS-PGA as explanatory variables. Odds ratios will be computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted. In case of response rates of 0% or of 100% in one of the treatment groups, Fisher's exact test will be applied. Risk difference and confidence intervals for risk difference will be provided. Multiple imputation will be applied in case of missing data and detail information will be specified in Statistical Analysis Plan.

Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item dermatology-specific HRQoL measure presented to each subject from the randomization up to the study end. The instrument contains six functional scales (i.e. symptoms and feeling, daily activities, leisure, work and school, personal relationships, treatment). Each question is answered with the following response: "not at all," "a little," "a lot," or "very much". 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: Decrease of ≥ 5.0 points on DLQI total score will be considered as responder and logistic regression will be utilized for analysis with treatment group, Hurley stage, geographical region, use of antibiotic, baseline bodyweight, baseline DLQI score as explanatory variables. Odds ratios and will be computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted. In case of response rates of 0% or of 100% in one of the treatment groups, Fisher's exact test will be applied. Risk difference and confidence intervals for risk difference will be provided. Multiple imputation will be applied in case of missing data and detail information will be specified in Statistical Analysis Plan.
- 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.
- To allow for a pairwise comparison between two secukinumab regimens and placebo until Week 16, DLQI score up to Week 16 will also be analyzed using a MMRM with treatment group, the respective baseline value, Hurley stage, use of antibiotic, geographical region, baseline bodyweight, visit, baseline DLQI*visit interaction, and treatment group*visit as covariates, with unstructured covariance matrix.

Work Productivity and Activity Impairment (WPAI)

Summary statistics will be provided for absolute and percentage change from baseline of WPAI component scores by visit up to end of study.

[redacted]

EQ-5D-3L

The EQ-5D is a questionnaire with 5 questions (regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each with three categories (no problem, moderate problem, severe problems) and a health state assessment from 0 (worst possible health state) to 100 (best possible health state). The number and percentage of subjects in each of the three categories for each question will be presented by visit up to the end of study for each treatment group. Summary statistics will be shown for the health state assessment by visit up to the end of study for each treatment group.

PGI (PGI-s and PGI-c)

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

HS Symptom Diary

Summary statistics will be provided for absolute and percentage change from baseline of HS symptom component scores and the absolute HS symptom component score by visit up to end of study.

Inflammatory markers with respect to CRP and ESR

Summary statistics will be provided for absolute and percentage change from baseline of CRP and ESR by visit up to end of study.

12.7 Interim analyses

[redacted]

Further details will be provided in DMC Charter and Statistical Analysis Plan.

[redacted]

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

Sample size requirements for this study are primarily driven by HiSCR at Week 16 endpoints. A 5% two-sided type-I-error rate will used to control for type I error. Two secukinumab doses will be tested versus placebo with respect to the primary endpoint (HiSCR at Week 16). The type-I-error will be split to 4% and 1% two-sided for secukinumab 300 mg q2w vs. placebo and secukinumab 300 mg q4w vs. placebo, respectively. Sample sizes will be based on this type-I-error assumption.

A total of 471 patients was originally planned to be randomized to study drug in a 1:1:0.5:0.5 ratio. A second study of identical design with the same sample size will be conducted in parallel. Both studies are independently powered to address the primary endpoint (HiSCR) and secondary endpoint on flare. The secondary endpoint on pain will be analyzed in the combined populations of both trials, provided the primary null-hypothesis can be rejected in both studies. All sample size calculations were done in nQuery Advisor 7.0.

As discussed in Section 5, to account for the disruptive impact of the COVID-19 pandemic on the conduct of the study since the release of protocol amendment 01, the number of randomized patients was increased to approximately 541 (15% increase from the original population of 471 patients).

12.8.1 Primary endpoint(s)

HiSCR: Based on adalimumab phase III placebo-controlled studies (PIONEER I and II, respectively, Kimball et al 2016), a placebo response rate of 30% is assumed. The original total sample size of 471 patients for this trial is sufficient to achieve 93% power for the demonstration of 20% difference of secukinumab 300 mg q2w over placebo based on the primary endpoint (HiSCR) when assuming a secukinumab response rate to be 50%. In regards to the comparison of secukinumab 300 mg q4w to placebo, we achieve 83% power to show superiority.

12.8.2 Secondary endpoint(s)

The power mentioned for the Secondary endpoints is conditional on the successful rejection of the null hypothesis for the primary endpoint (HiSCR), and the testing procedures are defined in Section 12.5.1.

Percentage change in AN count: based on adalimumab phase III placebo-controlled studies (PIONEER I and II, respectively (Kimball et al 2016), it is assumed that the difference between secukinumab and placebo is at least 18% in favor of secukinumab when considering the mean percentage change from baseline in AN count at Week 16. Although it is planned to use a repeated measures model for the analysis, an approximate sample size can be based on a simple t-test. The original sample size of 471 patients is sufficient to achieve 92% power in secukinumab 300 mg q2w vs. placebo and 81% power in secukinumab 300 mg q4w vs. placebo when assuming a standard deviation of 46%.

Flare: Based on adalimumab phase III placebo-controlled studies (PIONEER I and II, respectively, Kimball et al 2016), a placebo rate of 35% is assumed. The original sample size

[redacted]

of 471 patients is sufficient to achieve 98% power for the demonstration of 20% difference of secukinumab 300 mg q2w over placebo based on the second endpoint when assuming secukinumab 300 mg q2w rate to be 15%. Assuming the same rate for secukinumab 300 mg q4w, the sample size would be sufficient to achieve 92% power in a comparison of secukinumab 300 mg q4w vs. placebo.

Pain: Based on adalimumab phase III placebo-controlled studies (PIONEER I and II, respectively, Kimball et al 2016), a placebo rate of 23% is assumed. Assuming 80% patients are qualified to calculate Pain variable NRS30, the original total sample size of 942 patients across two studies is sufficient to achieve 85% power for the demonstration of 13% difference of secukinumab 300 mg q2w over placebo based on the second endpoint when assuming the rate to be 36%. The original sample size is also sufficient to achieve 70% power to demonstrate superiority of secukinumab 300 mg q4w over placebo based on the same assumptions in regards to the rates of secukinumab and placebo as above.

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 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.) .

[redacted]

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided 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

14 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.

14.1 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.

[redacted]

15 References

References are available upon request

Alavi A (2016) Discussion: What Heals Hidradenitis Suppurativa: Surgery, Immunosuppression, or Both? Plast. Reconstr. Surg. p. 230S-1S.

Andersen RK, Jemec GBE (2017) Pathophysiology of Hidradenitis Suppurativa p. 19-26.

Bettoli V, Join-Lambert O, Nassif A (2016) Antibiotic Treatment of Hidradenitis Suppurativa. Dermatol Clin p. 81-9.

Bretz F, Maurer W, Xi D. (2019) Replicability, reproducibility and multiplicity in drug development. CHANCE. p.4-11.

Bruin G, Loesche C, Nyirady J, et al (2017) Population Pharmacokinetic Modeling of Secukinumab in Patients With Moderate to Severe Psoriasis. J Clin Pharmacol p. 876-885.

Carpenter JR, Roger JH, Kenward MG (2013) Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat p. 1352-71.

Deckers IE, Kimball AB (2016) The Handicap of Hidradenitis Suppurativa. Dermatol Clin p. 17-22.

Deckers IE, van der Zee HH, Prens EP (2014) Epidemiology of Hidradenitis Suppurativa: Prevalence, Pathogenesis, and Factors Associated with the Development of HS. p. 54-60.

Dessinioti C, Zisimou C, Tzanetakou V, et al (2016) Oral clindamycin and rifampicin combination therapy for hidradenitis suppurativa: a prospective study and 1-year follow-up. Clin. Exp. Dermatol. p. 852-857.

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. p. 209-17.

Fimmel S, Zouboulis CC (2010) Comorbidities of hidradenitis suppurativa (acne inversa). Dermatoendocrinol p. 9-16.

Finlay AY, Khan GK (1994) Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin. Exp. Dermatol. p. 210-6.

Garcia-Montoya and Marzo-Ortega (2018) The role of secukinumab in the treatment of psoriatic arthritis and ankylosing spondylitis. Ther Adv Musculoskelet Dis.Sep 6;10(9):169-180.

Garg A, Kirby JS, Lavian J, et al (2017) Sex- and Age-Adjusted Population Analysis of Prevalence Estimates for Hidradenitis Suppurativa in the United States. JAMA Dermatol p. 760-764.

Horváth B, Janse IC, Blok JL, et al (2017) Hurley Staging Refined: A Proposal by the Dutch Hidradenitis Suppurativa Expert Group. Acta Derm. Venereol. p. 412-413.

Humira (adalimumab) EPAR.

[redacted]

Janse IC, Deckers IE, van der Maten AD, et al (2017) Sexual health and quality of life are impaired in hidradenitis suppurativa: a multicentre cross-sectional study. Br. J. Dermatol. p. 1042-1047.

Jemec GBE (2012) Clinical practice. Hidradenitis suppurativa. N. Engl. J. Med. p. 158-64.

Kelly G, Hughes R, McGarry T, et al (2015) Dysregulated cytokine expression in lesional and nonlesional skin in hidradenitis suppurativa. Br. J. Dermatol. p. 1431-9.

Kelly G, Sweeney CM, Tobin AM, et al (2014) Hidradenitis suppurativa: the role of immune dysregulation. Int. J. Dermatol. p. 1186-96.

Kimball AB, Ganguli A, Fleischer A (2018) Reliability of the hidradenitis suppurativa clinical response in the assessment of patients with hidradenitis suppurativa. J Eur Acad Dermatol Venereol. p. 2254-6.

Kimball AB, Jemec GBE, Yang M, et al (2014) Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. Br. J. Dermatol. p. 1434-42.

Kimball AB, Kerdel F, Adams D, et al (2012) Adalimumab for the treatment of moderate to severe Hidradenitis suppurativa: a parallel randomized trial. Ann. Intern. Med. p. 846-55.

Kimball AB, Okun MM, Williams DA, et al (2016) Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. N. Engl. J. Med. p. 422-34.

Lima AL, Karl I, Giner T, et al (2016) Keratinocytes and neutrophils are important sources of proinflammatory molecules in hidradenitis suppurativa. Br. J. Dermatol. p. 514-21.

Lipsker D, Severac F, Freysz M, et al (2016) The ABC of Hidradenitis Suppurativa: A Validated Glossary on how to Name Lesions. Dermatology (Basel) p. 137-42.

Manuel O, Kumar D (2008) QuantiFERON-TB Gold assay for the diagnosis of latent tuberculosis infection. Expert Rev. Mol. Diagn. p. 247-56.

Matusiak Ł, Szczęch J, Bieniek A, et al (2016) Increased interleukin (IL)-17 serum levels in patients with hidradenitis suppurativa: Implications for treatment with anti-IL-17 agents. J. Am. Acad. Dermatol. p. 670-675.

Newcombe RG (1998) Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med p. 857-72.

Pandey K, Sekhri R, Sekhri V (2018) IL-17 inhibitor Secukinumab in refractory Hidradenitis Suppurativa: A case report.

Revuz J (2009) Hidradenitis Suppurativa J Eur Acad Dermatol Venereol.Sep23;(9):985-98.

Sartorius K, Emtestam L, Jemec GBE, et al (2009) Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. Br. J. Dermatol. p. 831-9.

Schuch A, Fischer T, Boehner A, et al (2018) Successful Treatment of Severe Recalcitrant Hidradenitis Suppurativa with the Interleukin-17A Antibody Secukinumab. Acta Derm. Venereol. p. 151-152.

[redacted]

Storer MA, Danesh MJ, Sandhu ME, et al (2018) An assessment of the relative impact of hidradenitis suppurativa, psoriasis, and obesity on quality of life. Int. J. Women's Dermatology 4; 198–202.

Thorlacius L, Ingram JR, Villumsen B, et al (2018) A Core Domain Set For Hidradenitis Suppurativa Trial Outcomes: An International Delphi Process. Br. J. Dermatol.

Thorlacius L, Theut Riis P, Jemec GBE (2017) Severe hidradenitis suppurativa responding to treatment with secukinumab: a case report. Br. J. Dermatol.

Wolk K, Warszawska K, Hoeflich C, et al (2011) Deficiency of IL-22 contributes to a chronic inflammatory disease: pathogenetic mechanisms in acne inversa. J. Immunol. p. 1228-39.

Zouboulis CC, Desai N, Emtestam L, et al (2015) European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. J Eur Acad Dermatol Venereol p. 619-44.

Zouboulis CC, Tzellos T, Kyrgidis A, et al (2017) Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. Br. J. Dermatol. p. 1401-1409.

[redacted]

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

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 (ALP): > 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

Urinalysis

Protein urine dipstick: ++*

* ++ is ≥ 100 mg/dl

[redacted]

16.2 Appendix 2: Blood samples collection

Table 16-1 Blood log: Time schedule for blood sampling

		Hematology	Clinical Chemistry	Serum pregnancy test	Blood sample for PK		Blood sample for IG	Biomarker	TB test	Total volume (ml)
Period	Visit Name	Volume (ml)	Volume (ml)	Volume (ml)	Dose Ref. ID#	Volume (ml)	Volume (ml)	Volume (ml)	Volume (ml)	
Screening	Screening 1	4.8	3.5	2					4	14.3
	Screening 2									0
Treatment Period 1	Baseline	4.8	5		1	2	2	15		28.8*
	Week 1									0
	Week 2	4.8	3.5							8.3
	Week 3									0
	Week 4	4.8	3.5							8.3
	Week 8	4.8	3.5							8.3
	Week 12	4.8	3.5							8.3
	Week 16/EOT1	4.8	5		2	2	2	15		28.8
Treatment Period 2	Week 17									0
	Week 18	4.8	3.5							8.3
	Week 19									0
	Week 20	4.8	3.5							8.3
	Week 24				3	2				2
	Week 28	4.8	3.5							8.3
	Week 32									0
	Week 36									0
	Week 40									0
	Week 44	4.8	3.5							8.3
	Week 48									0
	Week 52/EOT2	4.8	5		4	2	2	15	4	32.8

[redacted]

Period	Visit Name	Hematology	Clinical Chemistry	Serum pregnancy test	Blood sample for PK		Blood sample for IG	Biomarker	TB test	Total volume (ml)
		Volume (ml)	Volume (ml)	Volume (ml)	Dose Ref. ID#	Volume (ml)	Volume (ml)	Volume (ml)	Volume (ml)	
Post-Treatment Follow-Up	Week 60	4.8	3.5		4	2	2			12.3

* For patients who sign optional DNA sampling ICF, 3 ml of blood will be additionally collected at baseline visit. # Dose reference IDs 1, 2 and 3 are collected pre-dose; scheduled post-dose time points for dose reference ID 4 are collected 2 and 10 weeks post-last study dose.

[redacted]

16.3 Appendix 3: Type I alpha for the pain hypothesis

Pain will be analyzed based on pooled data.Detailed information are listed in below table:

Table 16-2 Type I alpha for the pain hypothesis

		Hypothesis rejected within two studies					Alpha for pooled pain	
	300q2w HiSCR	**300q2w AN count**	**300q2w Flare**	**300q4w HiSCR**	**300q4w AN count**	**300q4w Flare**	**300q2w Pooled Pain**	**300q4w Pooled Pain**
Scenario	H_1, H'_1	H_3, H'_3	H_5, H'_5	H_2, H'_2	H_4,H'_4	H_6, H'_6	H_7	H_8
1	Y	N	N	N	N	N	$4\alpha/5-\alpha^2$	-
2	Y	Y	N	N	N	N	$4\alpha/5-\alpha^2$	-
3	Y	Y	Y	N	N	N	$4\alpha/5-\alpha^2$	-
4	N	N	N	Y	N	N	-	$\alpha/5-\alpha^2$
5	N	N	N	Y	Y	N	-	$\alpha/5-\alpha^2$
6	N	N	N	Y	Y	Y	-	$\alpha/5-\alpha^2$
7	Y	N	N	Y	N	N	$4\alpha/5-\alpha^2$	$\alpha/5-\alpha^2$
8	Y	Y	N	Y	N	N	$4\alpha/5-\alpha^2$	$\alpha/5-\alpha^2$
9	Y	Y	Y	Y	N	N	$4\alpha/5-\alpha^2$	$\alpha/5-\alpha^2$
10	Y	N	N	Y	Y	N	$4\alpha/5-\alpha^2$	$\alpha/5-\alpha^2$
11	Y	Y	N	Y	Y	N	$4\alpha/5-\alpha^2$	$\alpha/5-\alpha^2$
12	Y	Y	Y	Y	Y	N	$4\alpha/5-\alpha^2$	$\alpha/5-\alpha^2$
13	Y	N	N	Y	Y	Y	$4\alpha/5-\alpha^2$	$\alpha/5-\alpha^2$
14	Y	Y	N	Y	Y	Y	$4\alpha/5-\alpha^2$	$\alpha/5-\alpha^2$
15	Y	Y	Y	Y	Y	Y	$4\alpha/5$	$\alpha/5$

For scenario 1, 2 and 3, where H1, H'1 are rejected, and H2, H'2 are not rejected, then H7 could be tested at level $4\alpha/5-\alpha^2$, and H8 cannot be tested.

For scenario 4, 5 and 6, where H2, H'2 are rejected, and H1, H'1 are not rejected, then H8 could be tested at level $\alpha/5-\alpha^2$, and H7 cannot be tested.

For scenario 7 to 14, where H1, H'1, H2, H'2 are rejected, and at least one of the hypothesis H3, H'3, H4, H'4, H5, H'5 , H6, H'6 are not rejected, then H7 and H8 could be tested. Initially, H7 is tested at level $4\alpha/5-\alpha^2$ and H8 is tested at level $\alpha/5-\alpha^2$. If H7 (H8) is rejected, H8 (H7) can be tested at level $\alpha-2\alpha^2$.

For scenario 15 where H1, H'1, H2, H'2, H3, H'3, H4, H'4, H5, H5', H6, H6' are all rejected, then H7 and H8 could be tested at level α. Initially, H7 is tested at level $4\alpha/5$ and H8 is tested at level $\alpha/5$. If H7 (H8) is rejected, H8 (H7) can be tested at level α.

The subtraction of α^2 would be subtracted in the initial significance level for pain hypothesis (H7 and/or H8) is to account for the maximum possible type I error to claim a success for HiSCR, AN count and/or Flare in both studies. Therefore, the type I error rate is controlled at level α for the submission on all hypothesis endpoints. Under the global null hypothesis (i.e. no difference between secukinumab and placebo), the testing procedure outlined above controls

[redacted]

the type I error rate (one-sided) at the study-level to <0.025, and at the submission level to <0.000625(=0.025^2). Considering all possible configurations of true and false null hypotheses, the type I error control at the level of the submission is <0.000625 for the primary objectives, and <0.025 for all hypotheses (Bretz et al 2019).

[redacted]