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AIN457

Clinical Trial Protocol CAIN457M2301E1 / NCT04179175

A Multicenter, Double-blind, Randomized Withdrawal extension study of subcutaneous secukinumab to demonstrate long-term efficacy, safety and tolerability in subjects with moderate to severe hidradenitis suppurativa

Document type:	Amended Protocol Version
EUDRACT number:	2019-003230-17
Version number:	01 (Clean)
Clinical Trial Phase:	III
Release date:	28-May-2020

Table of contents

List of tables

List of figures

List of abbreviations

A	Abscess
AE	adverse event
ALT	alanine aminotransferase
AN	abscesses and inflammatory nodules
AST	aspartate aminotransferase
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulation
CO	Country Organization
COAs	Clinical outcome assessments
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CTT	Clinical trial team
CV	coefficient of variation
DF	Draining fistulae
[redacted]	[redacted]
DMC	Data Monitoring Committee
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EOT	end of treatment
[redacted]	[redacted]
F	Fistulae
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	hour
HiSCR	Hidradenitis Suppurativa Clinical Response
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
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
[redacted]	[redacted]
IL-17A	Interleukin-17A
IRB	Institutional Review Board
IRT	Interactive Response Technology
LOE	Loss of efficacy
LOR	Loss of response

LLN	lower limit of normal
MedDRA	Medical dictionary for regulatory activities
[redacted]	[redacted]
mRNA	messenger RNA
mg	milligram(s)
mL	milliliter(s)
ml	milliliter(s)
N	Inflammatory nodules
[redacted]	[redacted]
p.o.	Oral
[redacted]	[redacted]
PEA	Primary endpoint analysis
PFS	pre-filled syringe
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
q2w	once every two weeks
q4w	once every four weeks
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
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization
[redacted]	[redacted]
β-hCG	β-human chorionic gonadotropin

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.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
HiSCR response	Defined as at least 50% decrease in Abscess and inflammatory Nodule (AN) number with no increase in the number of abscesses and in the number of draining fistulae
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.
Loss of response	A 50% or greater increase in the abscess and/or inflammatory nodule (AN) count at a regular or unscheduled visit compared to the average AN count from the 3 previous visits (including core visit) or Week 52, whichever is lower, and the increase is at least 3 AN
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study, 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 subjects with established disease and in those with newly-diagnosed disease.
Subject	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.
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.

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.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term “Subject” may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable (or endpoint)	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of consent (WoC)	Withdrawal of consent from the study 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.

Amendment 1

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 assessment 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 as well as being monitored for safety in these situation. 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, the exclusion criterion #6 was added: this criterion was included in the protocols of the core trials, and therefore omitted in the previous version in the original protocol of the extension study. However, this edit follows the request from a few HAs, and ensures Investigators are re-evaluating subjects with concomitant disorders before the roll-over into the extension study.

The major changes made to the protocol are listed below.

- Section 2 has been edited with the addition of few sentences to better define the achievement of loss of response (LOR)
- Section 3, Section 6.7, Section 6.7.2, Section 8, Section 8.3 and 8.4 have been modified to allow study drug shipment to subjects, as well as remote contact to collect safety information, in case of pandemic/epidemic events.
- Sections 3.1.1, 3.2.1 and 6.3.1 have been edited to introduce flexibility in the ICF signature from the subject, consenting to participating in the extension phase.
- Section 5.2 has been edited adding one exclusion criteria limiting the participation to patients with underlying immunocompromising diseases.
- Section 6.3.2 has been re-worded to clarify the data entry process to be performed at Week 52 of the core studies, to qualify the patients entering the extension study.
- Section 6.4 has been updated to clarify additional events leading to the break of the blinding codes.
- Section 8 has been edited with the removal of serum pregnancy test at Week 52, replaced with urine pregnancy testing (accordingly, Section 8.4.3 has been modified).
- Section 11.3 has been edited to introduce remote monitoring activities, if appropriate.
- Section 12.4.3 and Section 12.8 have been modified to allow an extension of the recruitment if missing data due to a global health event jeopardize the power of the predefined statistical tests

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

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.

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.

Protocol summary

Protocol number	CAIN457M2301E1
Full Title	A Multicenter, Double-blind, Randomized Withdrawal extension study of subcutaneous secukinumab to demonstrate long-term efficacy, safety and tolerability in subjects with moderate to severe hidradenitis suppurativa
Brief title	Extension study to assess effects of non-interrupted versus interrupted and long term treatment of two dose regimens on efficacy and safety 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 extension study is to evaluate maintenance of HiSCR response at Week 104 in either continuous or interrupted therapy (using a randomized withdrawal period) of two dose regimens and to assess long-term efficacy, safety and tolerability of secukinumab in subjects with moderate to severe hidradenitis suppurativa (HS) completing either of the two Phase III studies, CAIN457M2301 or CAIN457M2302, both 52 weeks in duration. In addition this study will provide long-term access to the study medication.
Primary Objective(s)	The primary objective of this study is to demonstrate the efficacy of secukinumab (300 mg q4w or 300 mg q2w) in subjects with moderate to severe HS who were HiSCR responders at Week 52 of the core studies, with respect to loss of response by Week 104, compared to placebo.
Secondary Objectives	To assess the long-term safety and tolerability of secukinumab in subjects with moderate to severe HS evaluated by adverse events, abnormal laboratory values and vital signs.
Study design	This is a multicenter extension study to both core Phase III studies CAIN457M2301 and CAIN457M2302 (core studies). This study contains a randomized withdrawal design, double blinded and placebo controlled up to Week 104 or until loss of response is achieved. The subjects with HiSCR response after 52 weeks of treatment in the core studies will be randomized at 2:1 ratio to either continue on one of the two secukinumab dosing regimens assigned in core studies for another 52 weeks, or will be placed on placebo. The primary endpoint is loss of response (LOR) assessed during the 52-week treatment duration (up to Week 104). Subjects who attained LOR will be transferred to open-label treatment to continue until the end of the study. Subjects on placebo who did not reach LOR up to Week 104 will be offered to continue in the open-label treatment or discontinue the study. Thus for subjects who were HiSCR responders at Week 52 of core studies, the open label treatment duration will vary and start either from the time of LOR or from Week 104 dose and last until Week 260 followed by 8 weeks of a post treatment follow-up period to week 268. Subjects who were HiSCR non-responders at the end of core studies will be offered to continue in open-label treatment until Week 260.

	Subjects who prematurely discontinue the study, or who complete the study will enter a post-treatment follow up period (8 weeks)
Population	The study population will consist of subjects with moderate to severe HS who completed the core studies and choose to continue in the extension study. At Week 52 of the core studies subjects will be classified into HiSCR responders or non-responders. The eligible subjects will be recruited from the same sites as in the core studies
Key Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. 2. Subjects who complete the study treatment period (52 weeks) in the "Core studies" (CAIN457M2301 or CAIN457M2302) and were on secukinumab treatment during the Treatment Period 2 of the core studies
Key Exclusion criteria	1. A protocol deviation in the core study which, according to the investigator will prevent the meaningful analysis of the extension study for the individual subject 2. Ongoing or planned use of prohibited HS or non-HS treatments. Time of use of prohibited treatments in the core study must continue to be adhered to (see Table 6-2) 3. Subjects not expected to benefit from participation in the extension study, as assessed by the subject and investigator 4. Subjects whose participation in the extension study could expose them to an undue safety risk 5. Current severe progressive or uncontrolled disease which in the judgment of the investigator renders the subject unsuitable for the study 6. Underlying conditions (e,g chronic or recurrent systemic infections) which in the opinion of the investigator significantly immunocompromise the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy. 7. Plans for administration of live vaccines during the study
Study treatment	● Secukinumab 300 mg solution for s.c. injection in a 2 ml Pre-Filled Syringe (PFS) ● Placebo solution for s.c. injection in a 2 ml PFS
Efficacy assessments	Efficacy assessment related to the primary objective include: Individual lesion count used for calculation of Hidradenitis Suppurativa Clinical Response (HiSCR) and loss of response (LOR).
Key safety assessments	● Evaluation of all AEs and (Serious Adverse Event) SAEs ● Physical examination ● Vital signs ● Laboratory evaluations (e.g. hematology, clinical chemistry) ● Pregnancy
[redacted]	

	[redacted]
Data analysis	The primary endpoint of the study is time to loss of response up to Week 104 (randomized withdrawal period) in subjects who were HiSCR responders at Week 52 in the core studies. HiSCR response is defined as at least 50% decrease in Abscess and inflammatory Nodule (AN) number relative to the Baseline visit in the core study, with no increase in the number of abscesses and in the number of draining fistulae. Loss of response is defined as: • at least a 50% increase in AN (abscess and/or nodules) at a regular or unscheduled visits compared to the average AN count from 3 previous visits or the Week 52, whichever is lower, and the increase is at least 3 AN .• If at a regular or unscheduled visit, the subject experiences at least a 30% increase in AN compared to the average AN count from the 3 previous visits or the Week 52 whichever was lower with an increase of at least 2 AN from the average count of the 3 previous visits, the subject should be reassessed within 2-4 weeks. A further increase in the AN count of at least 2 AN would also be considered a LOR. Note: If 3 previous visits include visits from core studies, AN count from core studies will be included in the average. The secondary endpoints of this study are adverse events, laboratory values, and vital signs to assess the long-term safety and tolerability of secukinumab. The statistical hypothesis for the primary endpoint being tested is that the hazard rate is greater or equal in the secukinumab regimens versus placebo regimen. H1: The hazard rate of loss of response up to Week 104 is greater or equal in the Secukinumab 300 mg q2w group relative to the placebo group. H2: The hazard rate of loss of response up to Week 104 is greater or equal in the Secukinumab 300 mg q4w group relative to the placebo group. The primary analysis method will be a log-rank test, stratified by region and body weight stratum, to compare the survival functions between secukinumab treatment groups versus placebo. The hazard ratios for these comparisons for loss of response and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model with treatment group and baseline AN counts of extension study as explanatory variable and stratified by region and body weight stratum. Subjects who have not experienced loss of response up to Week 104 will be considered as censored observations. Summary statistics will be provided for all secondary endpoints.
Key words	hidradenitis suppurativa, HS, IL-17A, monoclonal antibody, AIN457, secukinumab, HiSCR, LOR, pain, efficacy, safety

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).

Hidradenitis suppurativa (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). Subjects 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 subjects 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).

In 2015, adalimumab (Humira®), a recombinant human monoclonal immunoglobulin G1 (IgG1) antibody to soluble and membrane bound tumour 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 subjects with HS and psoriasis, while levels in control and atopic dermatitis subjects 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 subjects with HS; a tendency toward higher serum concentrations of IL-17 has been reported for subjects 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 2019, over 27,000 patients have been enrolled in both completed and ongoing studies with secukinumab with over 22,000 having received active drug (Investigator's Brochure (IB) 19, data cut-off 25 Jun 2019). The cumulative subject exposure from post-marketing experience for all approved indications since the International Birth Date of the product is approximately 148,453 subject-treatment years (PTY) (Periodic Safety Update Report (PSUR) 5, data cut-off 25 Dec 2017). 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 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 subject 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 subject 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 subject with HS who responded to secukinumab treatment for a period of 6 months and was able to discontinue treatment after satisfactory improvement. The subject 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 subjects.

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 subjects with HS. The results of a randomized, double-blind, placebo-controlled Phase 2 study in 66 subjects 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 long-term efficacy, safety, [redacted] and tolerability of two dose regimens of secukinumab in subjects with moderate to severe HS in subjects who have completed the core trials (AIN457M2301 or AIN457M2302).

1.2 Purpose

The purpose of this extension study is to evaluate maintenance of response in either continuous or interrupted therapy (using a randomized withdrawal period) and to assess long-term efficacy, safety and tolerability of secukinumab in subjects with moderate to severe hidradenitis suppurativa (HS) completing either of the two Phase III studies, CAIN457M2301 or CAIN457M2302; both 52 weeks in duration. Primary endpoint analysis (PEA) of the extension study will be conducted on data collected at Week 104.

The data collected beyond Week 104 will deliver important information on the effect of long-term treatment of hidradenitis suppurativa with secukinumab. Additional analyses may be conducted at various time points for publications or Health Authorities interactions. Primary endpoint analysis at the end of the double-blind randomized withdrawal period will allow assessment of whether continuation of treatment with secukinumab brings benefit to subjects who already have been treated for one year in the preceding core studies in comparison to pausing the study treatment after clinical effect was achieved. In addition, data from the randomized withdrawal period will deliver important information on the effect of stopping

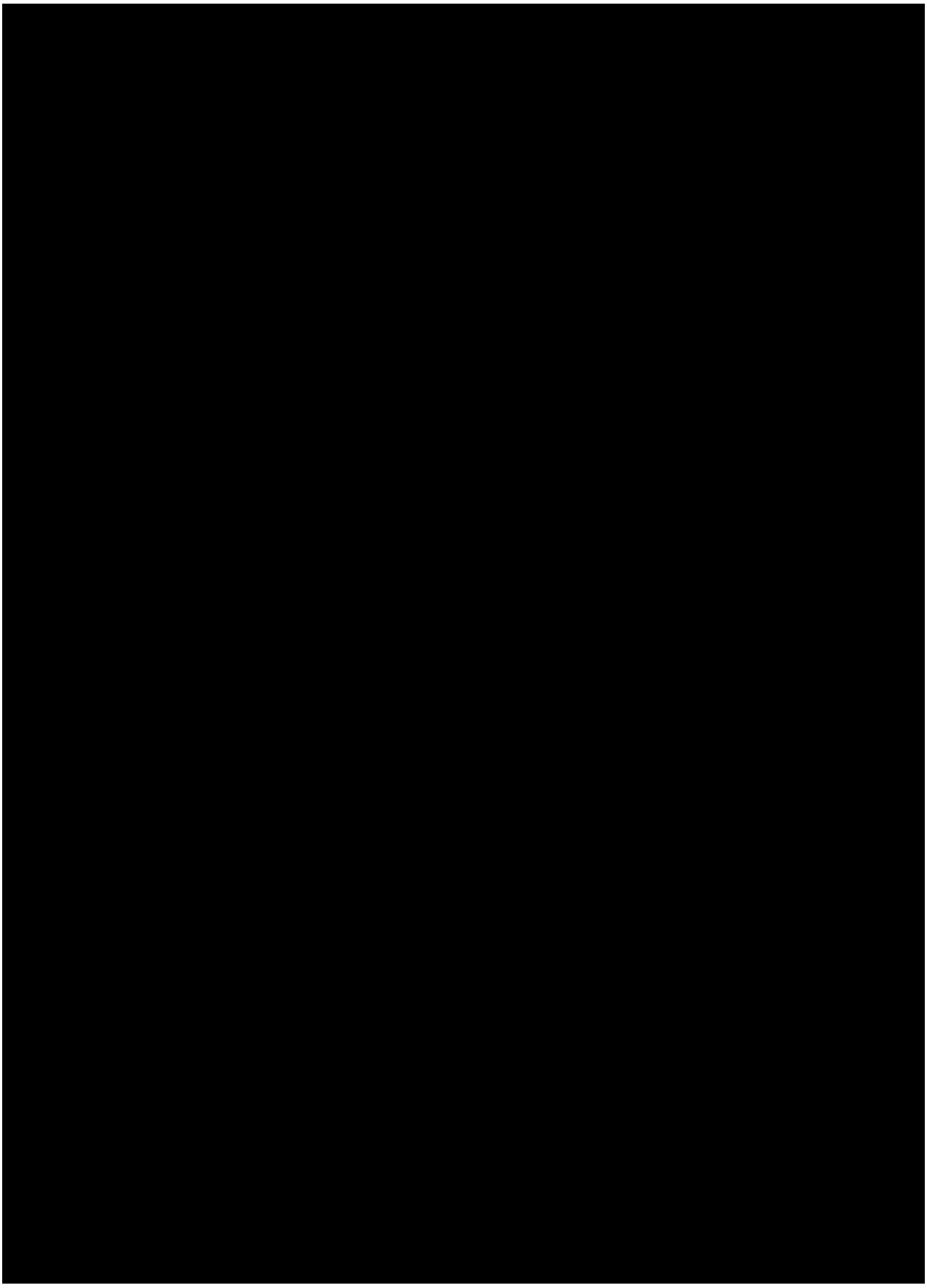
treatment on sustainability of clinical response. This analysis will include evaluation of time to loss of response, [redacted] Furthermore, this study will address the question of whether an increase in dose is effective in regaining and sustaining clinical response and a favorable risk-benefit ratio. The overall objective of the study is to determine efficacious and safe treatment strategies for long-term treatment of subjects suffering from this chronic disease.

The study will also offer subjects who completed treatment in the core studies an opportunity to have long-term access to HS therapy with secukinumab.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate the efficacy of secukinumab (300 mg q4w or 300 mg q2w) in subjects with moderate to severe HS who were HiSCR responders at Week 52 of the core studies, with respect to loss of response by Week 104, compared to placebo.	• Time to loss of response up to Week 104 (Randomized Withdrawal period) in subjects who were HiSCR responders at Week 52 in the core studies. HiSCR response is defined as at least 50% decrease in Abscess and inflammatory Nodule (AN) number relative to the Baseline visit in the core study, with no increase in the number of abscesses and in the number of draining fistulae. Loss of response is defined as: • at least a 50% or greater increase in AN count (abscess and/or nodules) at a regular or unscheduled visit, compared to the average AN count from 3 previous visits or the Week 52, whichever is lower, and the increase is at least 3 AN • If at a regular or unscheduled visit, the subject experiences at least a 30% increase in AN compared to the average AN count from the 3 previous visits or the Week 52 visit whichever is lower with an increase of at least 2 AN, the subject should be reassessed within 2-4 weeks. A further increase in the AN count of at least 2 AN would be considered a LOR also. Note: If the 3 previous visits include visits from core studies, the AN count from the core study will be included in the average.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the long-term safety and tolerability of secukinumab in subjects with moderate to severe HS.	• Adverse events, laboratory values, vital signs
[redacted]	



Objective(s)	Endpoint(s)
[redacted]	

3 Study design

This is a four year multicenter, double blind, randomized withdrawal extension study of two ongoing phase III studies CAIN457M2301 and CAIN457M2302 (collectively referred as the core studies). Total treatment time of the core and extension is up to five years.

This study will include a blinded and open-label part. The blinded part will include a placebo controlled period lasting up to 52 weeks (between Week 52 and Week 104) to provide data for randomized withdrawal analysis. The primary endpoint (PE) will be assessed at the Week 104 visit (End of Treatment (EOT-1) The duration of the randomized withdrawal period for each subject will be determined by the timepoint at which a subject has a loss of clinical response (LOR), as defined in Table 2-1. After LOR has been attained, the subject will receive open label treatment with secukinumab, and continue in the study for the maximum duration of 260 weeks of treatment plus 8 weeks of the post-treatment follow-up period in total, or until secukinumab is approved in the participating country. Starting from the time of LOR or Week 104 subjects will enter the open label part for an additional three years. The total duration of the extension study is estimated to last about four years providing up to approximately five years of total treatment exposure including the core study. For this protocol, years refers to the number of extension years (not core + extension) unless otherwise specified.

This study will include a blinded and open-label part. The blinded part will include a placebo controlled period lasting up to 52 weeks (between Week 52 and Week 104) to provide data for randomized withdrawal analysis. The primary endpoint (PE) will be assessed at the Week 104 visit (End of Treatment (EOT-1) The duration of the randomized withdrawal period for each subject will be determined by the timepoint at which a subject has a loss of clinical response (LOR), as defined in Table 2-1. After LOR has been attained, the subject will receive open label treatment with secukinumab, and continue in the study for the maximum duration of 260 weeks of treatment plus 8 weeks of the post-treatment follow-up period in total, or until secukinumab is approved in the participating country. Starting from the time of LOR or Week 104 subjects will enter the open label part for an additional three years. The total duration of the extension study is estimated to last about four years providing up to approximately five years of total treatment exposure including the core study. For this protocol, years refers to the number of extension years (not core + extension) unless otherwise specified.

It is expected that subjects who complete the four years of treatment will receive their final dose of study medication at Week 256 if randomized to the secukinumab 300 mg q4w dose regimen or at Week 258 if randomized to the secukinumab q2w dose regimen. Week 260 will be the end of the open label treatment (EoT2) followed by 8 weeks of the post treatment follow up period ending up at Week 268/F8 visit.

The study population will include subjects who have completed the entire treatment period in the core. Based on the Week 52 data from the core study, subjects will be defined as HiSCR responders or non-responders as follows:

- **HiSCR responders** (subjects who achieved at least 50% decrease in Abscess and Inflammatory Nodule (AN) number with no increase in the number of abscesses and in the number of draining fistulae) compared to the Baseline visit of the core study
- **HiSCR non-responders** (subjects who did not achieve at least 50% decrease in Abscess and Inflammatory Nodule (AN) number with no increase in the number of abscesses and in the number of draining fistulae) compared to the Baseline visit of the core study.

The study design for HiSCR responders and non-responders will be different.

The Week 52 visit in the core studies will be the randomization visit for CAIN457M2301E1 (called Week 52E1 in the extension study).

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.

3.1 HiSCR Responders at Week 52

For the subjects classified as HiSCR responders at Week 52 the study will consist of 4 periods.

3.1.1 Screening (Screening to Randomization)

There is no official screening period for this extension trial. Screening period is the duration between signing the informed consent form (ICF) and randomization registered with Interactive Response Technology (IRT). The screening will occur during the core studies. Subjects will be informed about the extension study during the core study and provided with the informed consent at a reasonable time point before the Week 52 visit. The ICF must be signed at the Week 52 visit for the subject to participate and be randomized into the extension trial, if they qualify.

3.1.2 Blinded Randomized Withdrawal Period (Randomization - LOR or up to Week 104, pre-dose) Year 1

Eligible subjects who are **HiSCR responders** at Week 52 of the core study and received the secukinumab 300 mg s.c. every other week (q2w) dosing regimen in the core studies up to Week 52, will be randomized in a 2:1 ratio to either **continue** the same s.c. doses of secukinumab as from the core studies or receive placebo s.c. The randomization will be stratified by region and body weight.

Subjects who were on 300 mg s.c. q2w in the core study will be randomized to:

a. Secukinumab 300 mg q2w group: One s.c. injection of secukinumab 300 mg at randomization (Week 52) and thereafter every 2 weeks up to Week 258.
b. Placebo secukinumab 300 mg q2w group: One s.c. injection of placebo secukinumab 300 mg at randomization (Week 52) and thereafter every 2 weeks up to Week 104 (or until loss of response LOR*).

Similarly, eligible subjects who were receiving the secukinumab 300 mg s.c. every four weeks (q4w) dosing regimen during the core studies up to Week 52, will be randomized in a 2:1 ratio

to either **continue** the same s.c. doses of secukinumab from the core studies or receive placebo s.c. The randomization will also be stratified by region and body weight.

a. Secukinumab 300 mg q4w group: One s.c. injection of secukinumab 300 mg at randomization (Week 52) and thereafter every 2 weeks alternating secukinumab and placebo until LOR* or until the end of randomized withdrawal period at Week 104.

b. Placebo secukinumab 300 mg q4w group: One s.c. injection of placebo secukinumab 300 mg at randomization (Week 52) and thereafter every 2 weeks up to Week 104 (or until LOR*).

*Loss of response (LOR) is defined as a 50% or greater increase in the abscess and/or inflammatory nodule (AN) count at a regular or unscheduled visit compared to the average AN count from the 3 previous visits (including visits from the core studies) or Week 52, whichever was lower, and the increase is of at least 3 AN.

If at a regular or unscheduled visit, the subject experiences a 30% or greater increase in AN count compared to the average AN count from 3 previous visits (including core visits) or the Week 52 whichever is lower with an increase of at least 2 AN the subject should be reassessed within 2-4 weeks. A further increase in the AN count of at least 2 AN would confirm disease progression and be considered LOR.

Subjects experiencing a LOR during the randomized withdrawal period (after Week 52 and until Week 104) will receive open-label treatment and the following dose regimen (re-induction and treatment thereafter):

(i). Secukinumab 300 mg q2w group:

Subjects who present with a loss of response (LOR) before Week 104 will receive two extra doses of placebo secukinumab 300 mg s.c. at 1 week and 3 weeks after the LOR was diagnosed (**dummy re-induction**). Starting at 4 weeks after LOR is diagnosed, the subject will continue on open-label secukinumab 300 mg q2w regimen until Week 258, or until the drug is approved in the participating country, whichever occurs first.

Subjects who do not present with LOR before Week 104 will complete the blinded randomized withdrawal period and will continue in the open-label treatment with secukinumab 300 mg q2w until Week 258 or until the drug is approved in the country, whichever occurs first. At Week 104, subjects will receive the first dose of the open-label treatment.

(ii). Placebo secukinumab 300 mg q2w group

Subjects who present with a loss of response (LOR) before Week 104 will receive five weekly secukinumab 300 mg s.c. starting at the visit where the LOR is diagnosed and then at 1 week, 2 weeks, and 3 weeks after the LOR (**re-induction**). Starting at 4 weeks after the LOR the subject will start on open-label secukinumab 300 mg q2w regimen throughout until Week 258.

Subjects who do not present with LOR before Week 104 will complete the blinded randomized withdrawal period and be unblinded, and eligible to enter the open-label treatment with secukinumab 300 mg q2w. Subjects who agree to continue in the open-label treatment will receive the first dose of secukinumab at Week 104 followed by four weekly doses (**re-induction**) and starting from Week 108 will continue on q2w dosing regimen until Week 258.

Subjects who do not agree to enter the open-label treatment, or who would not benefit from prolonging the treatment in the judgment of the Investigator, will be discontinued from the trial.

(iii). Secukinumab 300 mg q4w group

Subjects who present with a loss of response (LOR) before Week 104 will be up-titrated to secukinumab 300 mg s.c. q2w at the visit LOR is diagnosed with two extra placebo secukinumab 300 mg s.c. at 1 week and 3 weeks after the diagnose of LOR (**dummy re-induction**). Starting from week 4 after the LOR subjects will continue on the open-label secukinumab 300 mg q2w until Week 258 or until the drug is approved in the country, whichever occurs first.

Subjects who do not present with LOR until Week 104 will complete the blinded randomized withdrawal period and be unblinded, and eligible to enter the open-label treatment with secukinumab 300 mg q4w until Week 256 or until the IMP is approved in the country, whichever occurs first. At Week 104 they will receive the first dose of the open-label treatment. During the open-label period the investigator may decide to up-titrate the subjects to secukinumab 300 mg s.c. q2w based on clinical judgement.

(iv). Placebo secukinumab 300 mg q4w group

Subjects who present with a loss of response (LOR) before Week 104 will receive five weekly secukinumab 300 mg s.c. starting at the visit where the LOR is diagnosed, and then at 1 week, 2 weeks and 3 weeks after the LOR **(re-induction**). Starting at 4 weeks after the diagnosis of LOR, the subject will start the open-label secukinumab 300 mg s.c. q4w regimen until Week 256 or until IMP is approved in the country, whichever occurs first. During the open-label period the investigator may decide to up-titrate the subject to secukinumab 300 mg s.c. q2w based on clinical judgement.

Subjects who do not present with LOR before Week 104 will complete the blinded randomized withdrawal period, be unblinded and eligible to enter the open-label treatment with secukinumab 300 mg q4w. Subjects who agree to continue in the open-label treatment will receive the first dose of secukinumab at Week 104 followed by four weekly doses (**re-induction**) and starting from Week 108 will continue on q4w dosing regimen until Week 256 or until the investigator decided to up-titrate to secukinumab 300 mg s.c. q2w dosing regimen. Subjects who do not agree to enter the open-label treatment, or who would not benefit from prolonging the treatment in the judgment of the Investigator, will be discontinued from the trial.

During the blinded randomized withdrawal period all subjects will visit sites every eight weeks for the efficacy and safety assessments as shown in Table 8-1 and described in Section 8 and receive on-site injection of the study medication. The home-injections will take place every two weeks between the on-site visits to maintain q2w dosing regimen and placebo matching until Week 104/LOR. The LOR will be assessed by the investigator at every on-site visit and unscheduled visits if needed.

If the subject detects worsening of HS during the period between on-site visits, the subject will contact the investigator who will assess if an unscheduled visit is needed to evaluate LOR criteria. This unscheduled visit should be kept as close as possible to scheduled home-injections date. As re-induction is allowed only once during the randomized withdrawal period, if a subject

is diagnosed with clinical worsening after the LOR, the subject will receive additional "rescue" treatment for symptoms exacerbation at the discretion of investigator (see Section 6.2.3).

In the event of a pandemic/epidemic that limits or prevents the conduct of on-site study visits per protocol, special effort should be made for the on-site visits, scheduled and unscheduled, to assess LOR. If it is not feasible to conduct the LOR visits on site, virtual visits or visits to the patient`s home should be attempted by an adequately trained assessor. In case the LOR assessment is not possible and the patient reports worsening of HS signs and symptoms, which, in the judgement of the investigator, may be reasonably accounted as LOR, the patient will be given re-induction/dummy re-induction and be switched to the open label treatment as soon as possible.

3.1.3 Open Label Treatment Period (LOR/Week 104-up to Week 260)

Subjects will enter the open label period if they have attained LOR before Week 104 or at Week 104. In the open-label period, subjects taking secukinumab 300 mg s.c. q4w may be up-titrated to secukinumab 300 mg s.c. q2w based on clinical judgement without re-induction. The study medication can also be paused at investigator's discretion if this reflects local practice.

The frequency of the on-site visits in the open label period until Week 104 will remain every 8 weeks and, will be reduced to every 12 weeks after Week 104. After Week 104, depending on dosing regimen (q2w or q4w) the home-injections will be scheduled every two or every four weeks between the on-site injections visits. Similar to the randomized withdrawal period if the subject observes worsening of HS during the period between the on-site visits, the subject will contact the investigator who will assess if an unscheduled visit is needed to evaluate deterioration and initiate additional treatment as specified in Section 6.2 and / or up-titrate the study medication to q2w if needed. The definition of LOR will not be applied during the open-label period and the investigator will recognize clinical worsening requiring intervention in accordance to local practice. The need for down titration is not foreseen.

Subjects receiving secukinumab 300 mg q2w will receive the last injection at Week 258 and those on q4w dosing regimen at Week 256 or until IMP is approved in the country, whichever occurs first. The Week 260 visit will mark the end of the open label period (EoT-2). For subjects who completed the whole course of the open label period, and entered the post-treatment follow-up, Week 268/F8 visit will be the last visit in the study.

In the event of a global health disruptive event such as pandemic/epidemic (i.e Covid-19) that limits or prevents the conduct of on-site study visits, special effort should be made for the on-site visits scheduled and unscheduled to assess HS worsening. If it is not feasible to conduct on-site visits, virtual visits or visits to patient`s home should be attempted by an adequately trained assessor. In case the HS assessment is not possible and the patient reports worsening of HS signs and symptoms, the Investigator may consider an increase of the dose of the study medication from q4w to q2w and/or initiate additional treatment as specified in Section 6.2.

3.1.4 Post-Treatment Follow Up Period

Subjects who completed the open label treatment period will enter the post-treatment follow-up period after Week 260 visit and will return to the site 8 weeks later for the End of Follow up/Week 268 /F8 visit. This visit will mark the end of the study.

For subjects who do not intend to continue in the post-treatment follow-up or have withdrawn informed consent, the end of the study will be at the Week 260 (EoT-2) visit.

Subjects who prematurely discontinue from the study between Week 52 and Week 104 for any reason, will perform the Week 104 (EoT-1) visit and subsequently will enter the post-treatment follow-up period returning to the site 8 weeks later for the End of Follow-up/Week 268 /F8 visit. The Week 268 visit will be the last visit in the study (see Table 8-1). For subjects who do not intend to continue in the post-treatment follow-up or who have withdrawn informed consent, the end of the study will be at Week 104 (EoT-1) visit.

Similarly subjects who prematurely discontinue from treatment after Week 104 will have the Week 260 (EoT-2) visit performed at the time of discontinuation and return to the site 8 weeks later for the End of Follow-up/Week 268 /F8 visit (see Table 8-1). For subjects who do not intend to continue in the treatment-free follow-up or who have withdrawn informed consent, the end of the study will be at the Week 260/EoT-2 visit

3.2 HiSCR Non-Responders

For subjects classified as (HiSCR) non-responders at the end of the core trials (Week 52 of AIN457M2301 or AIN457M2302) the study will consist of 3 periods.

3.2.1 Screening (Screening to Randomization)

There is no official screening period for this extension trial. The screening will occur during core studies. Subjects will be informed about the extension study during the core study and provided with the informed consent at a reasonable time point before the Week 52 visit. The ICF must be signed at the Week 52 visit for the subject to participate and be enrolled into the extension trial, if they qualify.

3.2.2 Open Label Treatment Period Years 1 to 4 (Week 52-up to Week 260)

Subjects who are HiSCR non-responders at Week 52 of the core studies and intend to continue in the extension study will enter the open label treatment arm.

Subjects who received secukinumab 300 mg s.c. q2w or q4w at the end of the core study will continue on the secukinumab 300 mg s.c. q2w regimen. The decision to continue until the end of the study or to prematurely discontinue the subject will be left at the discretion of investigator.

Week 260 will be the end of treatment visit (EoT-2) in the open label treatment period.

3.2.3 Post-Treatment Follow up Period (8 weeks)

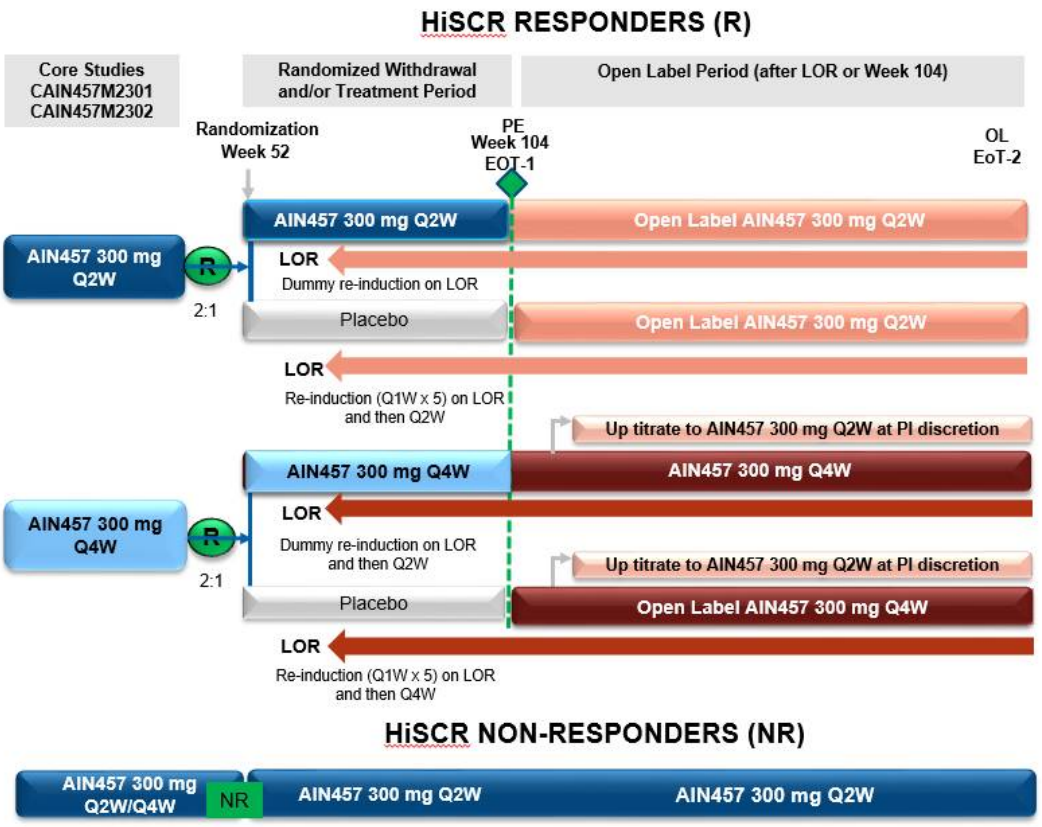
Subjects who completed the open label treatment period will enter the post-treatment follow-up period after the Week 260 visit and will return to the site 8 weeks later for the End of Follow up/Week 268 /F8 visit. This visit will mark the end of the study.

Subjects who prematurely discontinue from study treatment between Week 52 and Week 258 for any reason, will return for the Week 260 (EoT-2) visit after about 2 weeks following the last dose of the study medication and will return to the site 8 weeks later for the End of Follow-up /Week 268 /F8 visit. This will be the last visit in the study (see Table 8-1). For subjects who do

not intend to continue in the post-treatment follow-up or who have withdrawn informed consent, the end of the study will be the Week 260/EoT-2 visit.

The on-site visit frequency will be the same as of the HiSCR responders.

Figure 3-1 Study Design



In the event of a global health disruptive event such as a pandemic/epidemic (i.e Covid-19) that limits or prevents the conduct of on-site study visits, special efforts should be made to perform the assessments for the EoT-1/EoT-2 and End of the Follow/Week 268 up visits. If it is not feasible to conduct the EoT-1/EoT-2 and End of the Follow up/Week 268 visit on-site, virtual visits or visits to the patient´s home should be attempted, depending upon local regulations and capabilities.

4 Rationale

4.1 Rationale for study design

The natural history of the hidradenitis suppurativa is characterized by periods of worsening in severity and outbursts of flares, which are of different length and frequency. The disease is progressing over time with near diffuse or diffuse involvement of lesions and dermal tissue destruction leading to scar formation associated with restricted limb mobility (Yue Lee et al,

2017) critically impacting psychosocial functioning of subjects. Interruptions of treatment for various reasons are common in chronic diseases like hidradenitis suppurativa.

The main objective of this four-year multicenter, double-blind, randomized withdrawal extension study is to evaluate the effect of treatment interruption as well as re-treatment following interruption, on efficacy, tolerability and safety during the 52 week of maximal exposure to placebo and further to assess long-term efficacy and safety data up to 5 years of total exposure including core studies.

The concept of "randomized withdrawal" is in line with the International Council for Harmonization (ICH) Guidelines on Choice of Control Group and Related Issues in Clinical Trials, E10 (CPMP/ICH/364/96 2001), which recommends the design to evaluate effects of test treatment on relapse-prevention in recurring illness and where a long-term placebo-controlled trial would be difficult to establish long-term efficacy and safety. The maximum duration of placebo exposure of 52 weeks has been chosen to determine optimal cut-off for the primary endpoint analysis taking into consideration high placebo response rates after up to 24 weeks of treatment in PIONEER I and PIONEER II studies in hidradenitis suppurativa (Kimball et al 2016). Subjects who are still on placebo at Week 104 will be offered to be transferred to secukinumab open label treatment starting at Week 104 or may discontinue from the study. The primary endpoint in this study, the time to loss response (LOR) up to Week 104, has been selected to reflect the clinical practice. The loss of response (LOR) is defined as an 50% or greater increase of the abscess and inflammatory nodule (AN) count at regular or unscheduled visit compared to the average AN count from the 3 previous visits (including core visits) or Week 52, whichever was lower and the increase is at least 3 AN. If at a regular or extra visit, the subject had at least a 30% increase in AN count compared to the average AN count from the 3 previous visits (include core visits) or the Week 52, whichever is lower and the increase is at least 2 AN, the LOR will be considered if the subject had further increase in the AN count of at least 2 AN within the following 2 to 4 weeks. Because it is only reasonable to assess if subjects doing well can stop treatment or not, only subjects from one of the core studies with HiSCR at Week 52 and who are on study treatment, will be re-randomized into the randomized withdrawal period of this extension study.

Because time to LOR is the primary endpoint, subjects who achieve LOR during the randomized withdrawal period will be transferred to open-label treatment. Subjects who do not achieve LOR by Week 104 may start their open-label treatment at Week 104 including four weeks re-induction and continue with the dosing regimen they were receiving in the randomized treatment period or may discontinue from the study.

During the open-label period, the definition of LOR will not be applied and if the investigator determines clinical worsening, the subject may be started with intervention based on local practice. The subjects with clinical worsening who received q4w dosing regimen can be transferred (up-titrated) to higher dose (q2w) to evaluate if increasing the dose is of clinical benefit.

The decision to up-titrate the subjects to the higher dose will reside within the investigator`s clinical judgement to reflect normal clinical practice.

At Week 52 the allocation of HiSCR responders randomized to active treatment vs placebo will be 2:1 to reduce placebo exposure. The treatment blind will continue to be maintained for

individual subjects until (s)he reaches LOR or until the Week 104 pre-dose, to include all assessments needed for the primary endpoint data analysis. Starting from the Week 104 dose all subjects may continue on the open label treatments until Week 260 visit, which will mark the end of the treatment. After Week 260, subjects will enter the post-treatment follow-up period and visit the site 8 weeks later for the Week 268 /F8, which will mark the end of the study.

Subjects who do not attain HiSCR at Week 52 will not enter the randomized withdrawal period for the reasons discussed above. They will be given the possibility to continue on non-interrupted treatment regimen at the higher dose of secukinumab 300 mg s.c. q2w until the end of the treatment visit (EoT-2) at Week 260. After Week 260 subjects will enter the post-treatment follow-up period and visit the site 8 weeks later for the Week 268 /F8, which will mark the end of the study. The subjects who present with clinical worsening before the end of the study will receive additional treatment (non-secukinumab) at the investigator`s discretion or will be withdrawn from the study.

4.2 Rationale for dose/regimen and duration of treatment

The same secukinumab dosing regimen used in the core studies will be evaluated in this study:

- Secukinumab 300 mg s.c. every 4 weeks (q4w)
- Secukinumab 300 mg s.c. every 2 weeks (q2w)

Subjects in the non-interrupted treatment regimen and who switch from placebo to secukinumab following the LOR and regardless of the dosing frequency will start with a dummy re-induction/re-induction treatment consisting of five weekly 300 mg s.c. injections as described in Section 3. It is expected that the re-induction given to subjects switching from placebo to active treatment will help quickly achieve effective drug concentrations and lead to a more rapid onset of clinical response. As re-induction is not expected to bring similar effects if given to subjects in non-interrupted regimen, they will receive dummy re-induction following LOR in order to maintain blinding.

The 52-week maximum length of blinded randomization treatment period (from Week 52 until Week 104) was selected to ensure the study was adequately powered for the primary endpoint analysis (Section 12.4). Three year duration of the subsequent open label treatment period was selected in order to collect long-term safety and efficacy data reflecting normal clinical practice and up to the time point at which secukinumab is expected to receive approval in the participating country.

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

Use of placebo during withdrawal of active therapy in a randomized withdrawal study design until retreatment is necessary (in case of LOR) is in accordance with Health Authority Guidelines on Choice of Control Group in Clinical Trials (CPMP/ICH/364/96 2001). This is also supported by the fact that all subjects will have the opportunity to receive active treatment after experiencing the loss of response (LOR). All subjects who still sustained response until Week 104 while being on placebo will be offered to move to active treatment and receive their first secukinumab dose in the extension study at Week 104.

Because the study will use two secukinumab treatment regimen: 300 mg s.c. q2w and q4w matching placebo doses are needed during the blinded randomized withdrawal.

4.4 Purpose and timing of interim analyses/design adaptations

A primary endpoint analysis (PEA) of Week 104 data will be conducted after all subjects have completed Week 104 of treatment. Data for this analysis will be provided to address Health Authorities request to assess long-term efficacy, tolerability and safety data for interrupted and continuous treatment regimen.

Additional interim analyses may be conducted at various time points for publications or health authority's requests. Depending on the results of PEA from core studies one dose with an overall preferable benefit-risk ratio may be chosen and subjects who have been receiving the other dose regimen may be transferred to the chosen dose with a protocol amendment.

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.

Secukinumab therapy has a well-established and well-described safety profile based on extensive post-marketing experience and continued clinical trial exposure since 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.

The two ongoing phase III studies conducted in subjects with moderate to severe hidradenitis suppurativa will provide additional data on efficacy, tolerability and safety of two doses of secukinumab 300 mg, s.c. either at every two or every four week intervals in this indication.

The risk to subjects receiving placebo in the extension study CAIN457M2301E1 will be minimized by the study design. When a subject experiences a LOR during the randomized withdrawal period (Week 52 to Week 104), he/she will be assigned to the active treatment arm (secukinumab 300 mg s.c. either q2w or q4w).

All subjects will receive active treatment either from the start of the study, or after they have experienced loss of response. The maximum duration of placebo treatment is 52 weeks. All subjects on placebo after 52 weeks of treatment will be transferred to active treatment.

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 Data Monitoring Committee (DMC). The primary endpoint analysis in the core studies may recommend only one dose, which is expected to provide overall preferable risk/benefit ratio for subjects. In this case all subjects in the extension trial may be transferred to the dose recommended with a protocol amendment.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

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 CAIN457M2301E1.

5 Population

All subjects from studies CAIN457M2301 and CAIN457M2302 who have been receiving secukinumab treatment during Treatment Period 2, who completed the full study treatment period (52 weeks) in core studies and who comply with the inclusion and exclusion criteria of this study, are eligible to enter into extension study.

Assuming a drop-out rate of 21% up to Week 52 in both core studies, it is anticipated that approximately 745 subjects will come from the 2 core trials and be enrolled in the extension trial. Further assuming a HiSCR response rate at Week 52 of 45% in both the secukinumab 300 mg q2w arm and the secukinumab 300 mg q4w arm, 336 HiSCR responder subjects would be eligible to enter the randomized withdraw period.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Subjects who complete the whole study treatment period (52 weeks) in the core studies (CAIN457M2301 or CAIN457M2302) and have received secukinumab treatment during the Treatment Period 2 of the core studies.

5.2 Exclusion criteria

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

1. A protocol deviation in the core study which, according to the investigator will prevent the meaningful analysis of the extension study for the individual subject.
2. Ongoing or planned use of prohibited HS or non-HS treatments. Time of use of prohibited treatments in the core study must continue to be adhered to (see Table 6-2)
3. Subjects not expected to benefit from participation in the extension study, as assessed by the subject and investigator.
4. Subjects whose participation in the extension study could expose them to an undue safety risk.
5. Current severe progressive or uncontrolled disease which in the judgment of the investigator renders the subject unsuitable for the study.
6. 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.
7. Plans for administration of live vaccines during the study.
8. 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 subject. 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.
- 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 tubal ligation at least six weeks prior to enrollment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigation and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Secukinumab 300 mg	Solution for injection	Subcutaneous use	Double blinded subject packs; 2 ml pre-filled syringe	Sponsor (global)
Secukinumab 300 mg	Solution for injection	Subcutaneous use	Open label subject packs 2 ml pre-filled syringe	Sponsor (global)
Placebo-Secukinumab 300 mg	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-Secukinumab 300 mg 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 secukinumab matching placebo will be labeled as "AIN457 300 mg/Placebo", respectively, (2 ml) to keep the blind.

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

Subjects are requested to use over-the-counter antiseptics, Section 6.2.1.1.

6.1.3 Treatment arms/group

Eligible subjects who presented with HiSCR response at Week 52 visit and were receiving s.c.. secukinumab 300 mg q2w and s.c. secukinumab 300 mg q4w, will be assigned at the same visit to one of the following "4" treatment arms/groups in an active/placebo ratio of "2:1:2:1" respectively.

- **Secukinumab 300 mg q2w group:** subjects will receive first dose of secukinumab 300 mg s.c. at randomization (Week 52) and thereafter every 2 weeks (q2w) up to Week 258. To maintain the treatment blind subject will receive placebo doses 1 week, and 3 weeks after diagnosis of LOR (**dummy re-induction**).
- **Placebo Secukinumab 300 mg q2w group:** subjects will receive first dose of placebo secukinumab 300 mg s.c. at randomization (Week 52) and thereafter every 2 weeks (q2w)

up to Week 104 (or until loss of response LOR as described in Section 3). Subjects presenting with a LOR before Week 104 will switch to secukinumab 300 mg q2w with five weekly secukinumab 300 mg s.c. after diagnosis of LOR as re-induction. Subjects without LOR by Week 104 will be offered entry to the open-label treatment with secukinumab 300 mg q2w, after five weekly doses of re-induction starting from Week 104 or to discontinue from the study.

- **Secukinumab 300 mg q4w group:** subjects will receive first dose of secukinumab 300 mg s.c. at randomization (Week 52) and thereafter every 4 weeks up to Week 256 and placebo secukinumab every 4 weeks alternating with secukinumab starting at Week 54 until LOR or Week 104 as described in Section 3. Subjects presenting with a LOR before Week 104 will be up-titrated to secukinumab 300 mg q2w at the visit of the diagnosis of LOR with extra placebo secukinumab 300 mg s.c. 1 week and 3 weeks after diagnosis of LOR (**dummy re-inductions**); Subjects without LOR by Week 104 will continue secukinumab 300 mg q4w until Week 256. Subjects receiving open-label treatment can be up-titrated to secukinumab 300 mg q2w depending on clinical judgement.
- **Placebo secukinumab 300 mg q4w group:** subjects will receive first dose of placebo secukinumab 300 mg at randomization (Week 52) and thereafter every 2 weeks up to Week 104 (or until LOR as described in Section 3). Subjects presenting with a LOR before Week 104 will switch to secukinumab 300 mg q4w after five weekly doses of secukinumab 300 mg s.c. starting at the visit of the diagnose of LOR (**re-induction**). Subjects without LOR until Week 104 will be offered the opportunity to enter the open-label treatment with secukinumab 300 mg q4w, after five weekly doses of re-induction starting from Week 104 or may discontinue from the study. Subjects receiving open-label treatment can be up-titrated to secukinumab 300 mg q2w depending on clinical judgement.

Eligible subjects who do not present with HiSCR response at Week 52 visit will enter an additional open label arm as follows:

Subjects will receive secukinumab 300 mg every two weeks starting at Week 52 and up to Week 258.

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

6.1.4 Treatment duration

CAIN457M2301E1 is the extension study to two core studies, CAIN457M2301 and CAIN457M2302, each of 52 weeks planned treatment duration. This extension study is adding an additional 4 years of treatment (208 weeks). The planned total duration of treatment including core study is 260 weeks plus 8 weeks of the post-treatment follow-up or until secukinumab becomes approved in a participating country, whichever occurs first. Subjects may be discontinued from treatment earlier due to unacceptable toxicity or at the discretion of the investigator or the subject.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator must consider the baseline and ongoing concomitant treatment in core study (CAIN457M2301 or CAIN457M2302) before the subject enters the extension study (CAIN457M2302E1). Therapies reported on electronic Case Report Form (eCRF) pages (e.g. prior and concomitant medication, prior and concomitant non-drug therapies, topical steroid therapy) as ongoing at Week 52 of the core studies will be perceived as concomitant therapies for the extension study. Hence all concomitant therapies that were ongoing from the core study at Week 52 randomization visit will be followed in the extension study on the applicable concomitant medication or concomitant non-drug therapies eCRF pages.

The investigator must instruct the subject to notify the study site about any new medications taken after enrolling in the study. All 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 Case Report Forms.

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

6.2.1.1 Permitted concomitant therapy

Antiseptic Therapy

Subjects should be instructed to continue use of 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 diseases both related or unrelated to HS (e.g. pneumonia, cellulitis) are allowed as medically warranted during the study following local practice.

Topical and systemic antibiotics for the treatment of HS related symptoms are not allowed in the randomized withdrawal period up to LOR with exception for the rescue therapy. After LOR the use of antibiotics is not restricted and if in the investigator`s opinion they are clinically mandated the use of topical and systemic antibiotics should follow local guidelines.

Use of topical and systemic antibiotics is not restricted during the open-label treatment for both subjects groups: HiSCR responders and non-responders.

Analgesics

Non-opioid analgesics at prescribed doses are allowed to control HS and non-HS related pain.

Opioid analgesics are not allowed to treat HS during the randomized withdrawal period up to LOR.

If HS-related pain is uncontrolled with non-opioid analgesics at their maximal dose as per local label, 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 tramadol should be recorded by the subject in the eDiary and reviewed by the investigator at the scheduled visits.

For non-HS related pain opioid analgesics are permitted as per local practice but should be avoided if possible.

Use of opioid analgesics to treat HS symptoms is allowed during the open-label treatment for both subjects groups: HiSCR responders and non-responders per local practice.

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-2 that could confound the efficacy assessment or could put the subject at an additional safety risk are not allowed during the study and wash-out 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	Use between randomization and last dose of study drug	Action taken
Systemic biological immunomodulating treatment (e.g. adalimumab, infliximab, ustekinumab, anakinra, natalizumab)	Not allowed	Discontinue use or discontinue study treatment
Systemic non-biologic immunomodulating treatment (e.g. methotrexate (MTX), cyclosporine A, retinoids, apremilast)	Not allowed	Discontinue use or discontinue study treatment
Systemic corticosteroids for the treatment of HS**	Not allowed	Discontinue use or discontinue study treatment
Topical and systemic antibiotics for the treatment of HS	Not allowed until Week 104, except for rescue treatment and after LOR	Discontinue use or discontinue study treatment if not medically warranted

Medication	Use between randomization and last dose of study drug	Action taken
Opioid analgesics for HS*	Not allowed in the randomized withdrawal period up to LOR	Discontinue use or discontinue study treatment
Live vaccines	Not allowed	Discontinue study treatment
Surgeries for the treatment of HS other than allowed as rescue therapy during the randomized withdrawal period	Not permitted in the randomized withdrawal period up to LOR	Discontinue study treatment
Any investigational treatment or participation in any interventional trial	Not allowed	Discontinue study treatment

*analgesics permitted for non-HS related treatment

**allowed for the OL treatment

6.2.3 Rescue medication

Antibiotics

For HiSCR Responders:

Rescue therapies are allowed to treat acute flares or worsening of HS meeting criteria of LOR. During the randomized withdrawal period, subjects who qualify for rescue medication may initiate antibiotic treatment as per local guidance. Rescue antibiotic therapy should be captured in the source and on the appropriate eCRF. After Week 104 the use of antibiotics for treatment of HS is not restricted.

For HiSCR non-responders:

The investigator may offer rescue medication to subjects in the open-label treatment any time if medically warranted. The rescue medications will not be limited to antibiotics only and can be used in accordance to the local practice excluding prohibited medications.

Lesion Intervention

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

Other HS related surgery is not allowed during the randomized withdrawal period until LOR. They are not restricted during the open label treatment.

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

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Subjects in the extension study CAIN457M2301E1 will be assigned a uniquely identified subject number for the extension study. The uniquely identified subject number is composed by the study identifier (CAIN457M2301E1), 4-digit study site identifier assigned by Novartis for the site and a 3-digit sequential number assigned by the EDC system (e.g,

CAIN457M2301E1_1234001). Subjects who are eligible (as decided by the investigator or designee) based on the inclusion/exclusion criteria will be given the extension ICF at a reasonable timepoint prior to Week 52 to review and asked to sign the ICF after completing all assessments due at Week 52 of the core study.

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

6.3.2 Treatment assignment, randomization

At the end of Week 52 visit in the core study the investigator or his/her delegate will complete Week 52 assessments, verify inclusion/exclusion criteria, enter this information into the EDC to receive the subject ID then contact the IRT to provide HiSCR response status. 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 subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis 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 and body weight (weight < 90kg / ≥ 90kg). Subjects in the q2w arm will be randomized in a 2:1 ratio to either continue on q2w dosing or placebo. The same ratio of 2:1 will be applied for subjects in the q4w arm when randomized either to continue on q4w dosing or placebo.

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 in the randomized withdrawal period from the time of randomization until database lock for the Week 104 primary endpoint analysis*, using the following methods:

1. Randomization data will be 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

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

*The only exception to this, is represented by subjects on placebo who have not attained LOR by Week 104, as it may not be appropriate to switch these subjects free from treatment for one year to active treatment. They will be selectively unblinded at Week 104 to allow them to decide whether to enter the open-label treatment, or to discontinue from the study.

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

Unblinding for subjects, investigators/site personnel and Novartis personnel working directly with the sites, will only occur prior to database lock for Week 104 PEA in the case of subject emergencies (see Section 6.6.3). The appropriate personnel from the study site and Novartis will assess whether the study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

For the purpose of the Week 104 primary endpoint analysis, designated Novartis personnel involved in the study will be unblinded to the study treatment in the randomized withdrawal treatment period.

In case the results of the core studies are published while the extension study is still ongoing in a blinded manner, the data will be published in groups only, with limited ability to unblind subjects (The exception to this might be rare events that, if occurring in only one treatment group, would allow unblinding of the affected subjects). However, since this would be relevant to only a very small group of subjects, if any, no impact on the overall validity of the extension study is expected.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments are not permitted except for the scenarios described in Section 3.

6.5.1 Dose modifications

These dose changes must be recorded on the appropriate CRF.

During the randomized withdrawal period 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. In addition to the above, during the open-label period the treatment may be interrupted at the investigator's discretion.

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 subject's returned PFS should be collected for compliance checks by field monitors.

[redacted]

6.6.2 Recommended treatment of adverse events

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

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

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject for safety reasons.

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 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 8 weeks if on blinded medication, or 12 weeks if on open label medication, or more frequently if needed) will occur between the site and the 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

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

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
- 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 randomization visit at Week 52 after the inclusion/exclusion criteria have been confirmed and all study scheduled assessments have been performed. All study assessments, including completion of [redacted] 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.

Home administrations (H) should be done at pre -defined visits (see Table 8-1 and Section 6.6.1). 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 subjects 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.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation) Institutional Review Board (IRB)/Independent Ethics Committee (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 Good Clinical Practice (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 Core Date Sheet (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.

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.

8 Visit schedule and assessments

The assessment schedule (Table 8-1) lists all of the assessments mandatory for the study. All data obtained from these assessments must be supported in the subject's source documentation. Study visits and indicates with an "X" when the assessments are to be performed. All data obtained from these assessments must be supported in the subject's source documentation. An "S" indicates the data for that assessments are only in the source documents at the site.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study treatment for any reason should be scheduled for End of Treatment (EoT-1 and /or EoT-2) visit as soon as possible, at which time all of the assessments listed for the visit will be performed. At this visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Informed consent must be obtained prior to performing any study-related assessments or collecting any data for the Baseline/Week 52 visit, despite some of the assessments as indicated in Table 8-1 belonging to Week 52 visit of the core studies.

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.

Subjects who discontinue study treatment before completing the study should be scheduled for an end of treatment visit 2 weeks (wherever possible) after their last study treatment administration, at which time all the assessments listed for EOT-1 (Week 104)/EOT-2 (Week 260), as appropriate, will be performed. Subjects should then return to the study site 8 weeks after completing the EOT-1 or EOT-2 visit for the Follow-Up Week 268 /F8 visit for final safety and efficacy assessments. At the end of treatment visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

If a subject refuses to return for these assessments or is 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 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 [redacted] sample collection, vital signs measurements), study treatment administration.

Subjects who complete the study will attend the end of the treatment (EoT-2) visit and enter post-treatment follow up period ending at Week 268/F8 which will mark the end of the study.

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 8 weeks if on blinded treatment and every 12 weeks if on open label treatment 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, EOT-2/Week 268/F8 visits. If it is not feasible to conduct these visits on-site, phone calls should be attempted instead.

Table 8-1 Assessment Schedule

Period	Treatment Withdrawal									
Visit Name	**Week 52E1**[2]	**Week 60**	**Week 68**	**Week 76**	**Week 84**	**Week 92**	**Week 100**	**EOT-1 Week 104**[3]	**Unscheduled**	**Unscheduled LOR**[†]
Visit Numbers[1]	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**
Days	**365**	**421**	**477**	**533**	**589**	**645**	**701**	**729**	**unscheduled**	**unscheduled**
Visit at the site	X	X	X	X	X	X	X	X	X	X
Informed consent	X									
Inclusion / Exclusion criteria	X									
Demography	X									
Hurley stage	X[2]							X		X[11]
Physical Examination	S[2]							S		
Body Weight	X[2]							X		X[11]
Vital Signs	X[2]	X	X	X	X	X	X	X		X
Concomitant medications	X[2]	X	X	X	X	X	X	X		X
Adverse Events	X[2]	X	X	X	X	X	X	X		X
[redacted]										
Lesion count (subject)	X[2]	Complete monthly in eDiary								
Lesion count (Physician)	X[2]	X	X	X	X	X	X	X		X
Loss of Response (LOR)[4]		X	X	X	X	X	X	X		X

Period	Treatment Withdrawal									
Visit Name	**Week 52E1[2]**	**Week 60**	**Week 68**	**Week 76**	**Week 84**	**Week 92**	**Week 100**	**EOT-1 Week 104[3]**	**Unscheduled**	**Unscheduled LOR[+]**
Visit Numbers[1]	**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**
Days	**365**	**421**	**477**	**533**	**589**	**645**	**701**	**729**	**unscheduled**	**unscheduled**
[redacted]										
HiSCR score	X									
[redacted]										
Clinical chemistry	X[2]	X	X	X	X	X	X	X	X	X
Hematology	X[2]	X	X	X	X	X	X	X	X	X
Urine pregnancy test[8]	S[2]			S				S	S	
[redacted]										
Contact IRT	X	X	X	X	X	X	X	X		X
Randomization	X									
Drug dispensation	X	X	X	X	X	X	X	X		X
Drug Administration[5,6]	X	X	X	X	X	X	X	X		X
Period Completion/disposition form								X		
Health care resource utilization	X[2]	X	X	X	X	X	X	X		
Trial Feedback Questionnaire (optional)	X[2]							X		

Period	Extension Treatment 2 (Year 2 - 4)									
Visit Name	**Week 108**	**Week 120**	**Week 132**	**Week 144**	**Week 156**	**Week 168**	**Week 180**	**Week 192**	**Week 204**	**Week 216**
Visit Numbers[1]	**200**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**
Days	**757**	**841**	**925**	**1009**	**1093**	**1177**	**1261**	**1345**	**1429**	**1513**
Visit at the site	X	X	X	X	X	X	X	X	X	X

Period	Extension Treatment 2 (Year 2 - 4)									
Visit Name	**Week 108**	**Week 120**	**Week 132**	**Week 144**	**Week 156**	**Week 168**	**Week 180**	**Week 192**	**Week 204**	**Week 216**
Visit Numbers[1]	**200**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**
Days	**757**	**841**	**925**	**1009**	**1093**	**1177**	**1261**	**1345**	**1429**	**1513**
Informed consent										
Inclusion / Exclusion criteria										
Demography										
Hurley stage					X				X	
Physical Examination										
Body Weight					X				X	
Vital Signs	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
[redacted]										
Lesion count (subject)	Complete monthly in eDiary									
Lesion count (Physician)	X	X	X	X	X	X	X	X	X	X
Loss of Response (LOR)[4]										
[redacted]										
Clinical chemistry	X	X	X	X	X	X	X	X	X	X

Period	Extension Treatment 2 (Year 2 - 4)									
Visit Name	**Week 108**	**Week 120**	**Week 132**	**Week 144**	**Week 156**	**Week 168**	**Week 180**	**Week 192**	**Week 204**	**Week 216**
Visit Numbers[1]	**200**	**210**	**220**	**230**	**240**	**250**	**260**	**270**	**280**	**290**
Days	**757**	**841**	**925**	**1009**	**1093**	**1177**	**1261**	**1345**	**1429**	**1513**
Hematology	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[8]			S		S		S		S	
[redacted]										
Contact IRT	X	X	X	X	X	X	X	X	X	X
Randomization										
Drug dispensation	X	X	X	X	X	X	X	X	X	X
Drug Administration[5,6]	X	X	X	X	X	X	X	X	X	X
Period Completion/disposition form										
Health care resource utilization										
Trial Feedback Questionnaire (optional)					X				X	

Period	Extension Treatment 2 (Year 2 - 4)					
Visit Name	**Week 228**	**Week 240**	**Week 252**	**Week 260 EOT-2** [10]	**Unscheduled HS Assessment**	**F-U Week 268/ F8**
Visit Numbers[1]	**300**	**310**	**320**	**330**	**340**	**1999**
Days	**1597**	**1681**	**1765**	**1821**	**Unscheduled visit/ unscheduled HS Assessment**	**1877**
Visit at the site	X	X	X	X	X[7]	X
Informed consent						
Inclusion / Exclusion criteria						
Demography						
Hurley stage				X	X[7]	
Physical Examination				S		S
Body Weight				X	X[7]	
Vital Signs	X	X	X	X	X[7]	X

Period	Extension Treatment 2 (Year 2 - 4)					
Visit Name	**Week 228**	**Week 240**	**Week 252**	**Week 260 EOT-2 [10]**	**Unscheduled HS Assessment**	**F-U Week 268/ F8**
Visit Numbers[1]	**300**	**310**	**320**	**330**	**340**	**1999**
Days	**1597**	**1681**	**1765**	**1821**	**Unscheduled visit/ unscheduled HS Assessment**	**1877**
Concomitant medications	X	X	X	X	X[7]	X
Adverse Events	X	X	X	X	X[7]	X
[redacted]						
Lesion count (subject)	Complete monthly in eDiary	Complete monthly in eDiary		X		
Lesion count (Physician)	X	X	X	X	X[7]	X
Loss of Response (LOR)[4]						
[redacted]						
clinical chemistry	X	X	X	X	X	X
Hematology	X	X	X	X	X	X

Period	Extension Treatment 2 (Year 2 - 4)					
Visit Name	**Week 228**	**Week 240**	**Week 252**	**Week 260 EOT-2 [10]**	**Unscheduled HS Assessment**	**F-U Week 268/ F8**
Visit Numbers[1]	**300**	**310**	**320**	**330**	**340**	**1999**
Days	**1597**	**1681**	**1765**	**1821**	**Unscheduled visit/ unscheduled HS Assessment**	**1877**
Pregnancy test (urine)	S					
Contact IRT	X	X	X	X	X[7]	
Randomization						
Drug dispensation	X	X	X		X[7]	
Drug Administration[5,6]	X	X	X		X[7]	
Period Completion/disposition form				X		X
Health care resource utilization						
Trial Feedback Questionnaire (optional)				X		

Period	Extension Treatment 2 (Year 2 - 4)					
Visit Name	Week 228	Week 240	Week 252	Week 260 EOT-2 [10]	Unscheduled HS Assessment	F-U Week 268/ F8
Visit Numbers[1]	300	310	320	330	340	1999
Days	1597	1681	1765	1821	Unscheduled visit/ unscheduled HS Assessment	1877

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

†Visit to be performed if Loss of Response (up to week 104) is identified between scheduled visits.
[1] Visit structure given for internal programming purpose only
[2] Week 52 AIN457M2301E1 is the same Week 52 in the core trials. Data should be recorded once in the core trial database.
[3] HiSCR responders subjects that discontinue prior to Week 104 should complete Week 104/EoT-1 and the Week 268 F8 visit.
[4] After Week 104, the definition of LOR will not be applied. LOR will be collected from Week 52 to Week 104. LOR will not be applied in the open label period.
[5] Home administration will be performed at Weeks 54, 56, 58, 62, 64, 66, 70, 72, 74, 78, 80, 82, 86, 88, 90, 94, 96, 98, 102,105, 106, 107, 110, 112, 114, 116, 118, 122, 124, 126, 128, 130, 134, 136, 138, 140, 142, 146, 148, 150, 152, 154, 158, 160, 162, 164, 166, 170, 172, 174, 176, 178, 182, 184, 186, 188, 190, 194, 196, 198, 200, 202, 206, 208, 210, 212, 214, 218, 220, 222, 224, 226, 230, 234, 238, 242, 244, 246, 248, 250, 254, 256, 258. In addition, home administration will be required during re-induction/dummy re-induction after LOR identified or Week 104 visit (if LOR has not occurred). Home administration 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
[6] Re-induction with weekly doses for 4 weeks will follow LOR or Wk 104 (if no LOR has occurred) is described in Section 3
[7] Perform assessments only when the unscheduled visit occurs due to HS symptoms
[8] In case of positive urine pregnancy test result, study treatment must be interrupted and the pregnancy confirmed with serum pregnancy test done at central lab.

[redacted]

[10] Subjects who discontinue from open label treatment at any time should complete Week 260/EoT-2 and the Week 268 F8 visit
[11] If LOR is recognized at the scheduled visit, Hurley stage and body weight to be done.

8.1 Screening

Since subjects must have completed 52-weeks in the core trials (CAIN457M2301 or CAIN457M2302) there is no formal screening for this trial.

8.2 Subject demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with the CRF. The investigators must consider the baseline data of the core study for the Demography eCRF at Week 52/randomization visit before a subject enters the extension study. Subject demographics and baseline characteristics to be collected on all subjects include: age, gender, race, ethnicity, prior HS medications and therapy, and relevant medical history, current medical conditions present before signing informed consent. The demographic data of the extension study will be the same as demographic data of the core study.

8.2.1 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 (worst score).

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

8.3 Efficacy

In the event of a pandemic/epidemic that limits or prevents on-site study visits, selected efficacy assessments (excluding AN count to determine LOR) 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.

[redacted]

8.3.1 Hidradenitis Suppurativa Clinical Response (HiSCR)

HiSCR response (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 fistula (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.

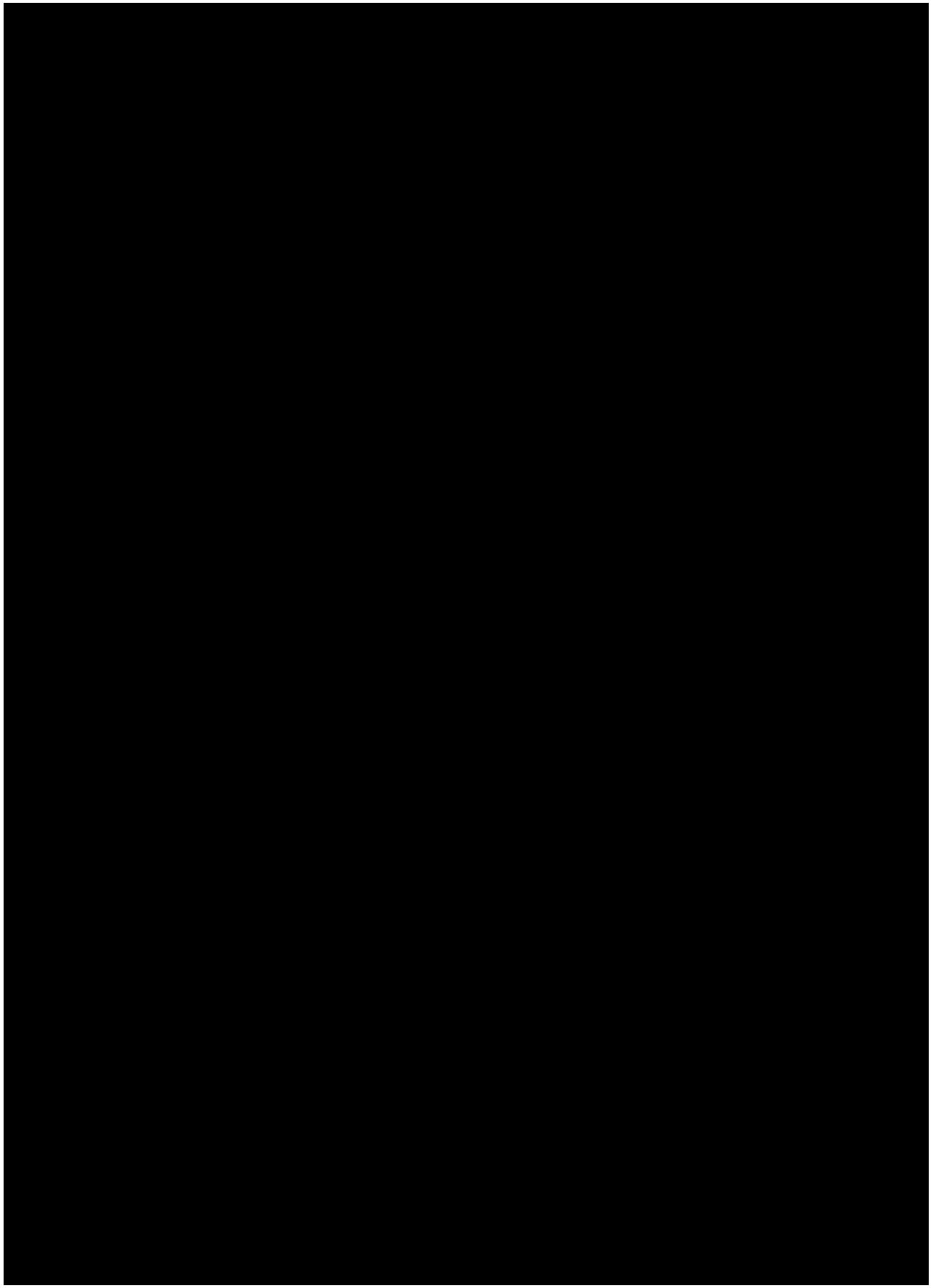
Individual lesion count

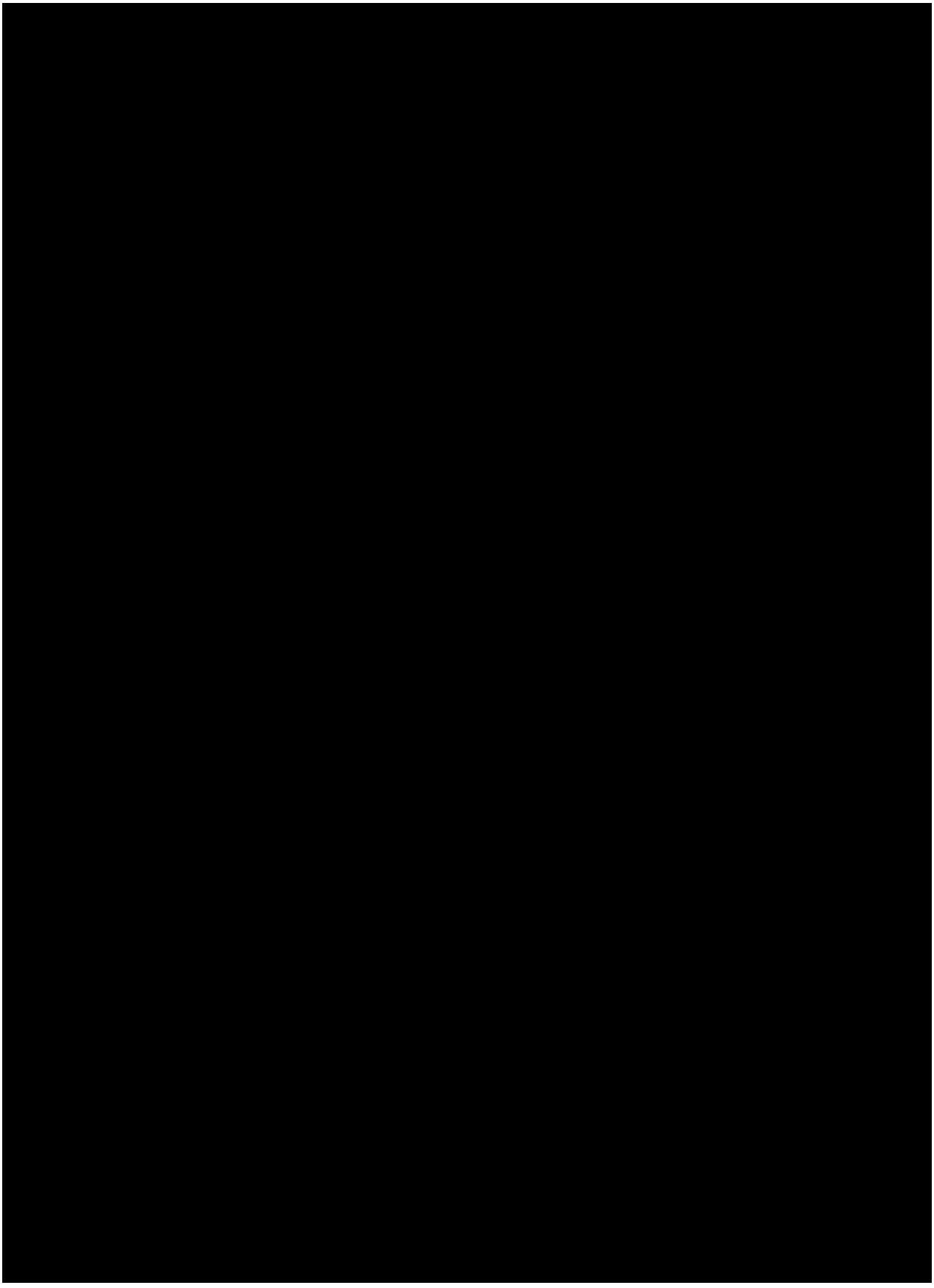
The HS affected areas, e.g. right and left axillary (armpit), right and left gluteal ("buttock"), right and left inguinal-femoral (groin), perineal, pubic, sternal, right and left sub-mammary (breast) and others will be assessed by the physician for abscesses, inflammatory nodules, draining fistulas,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

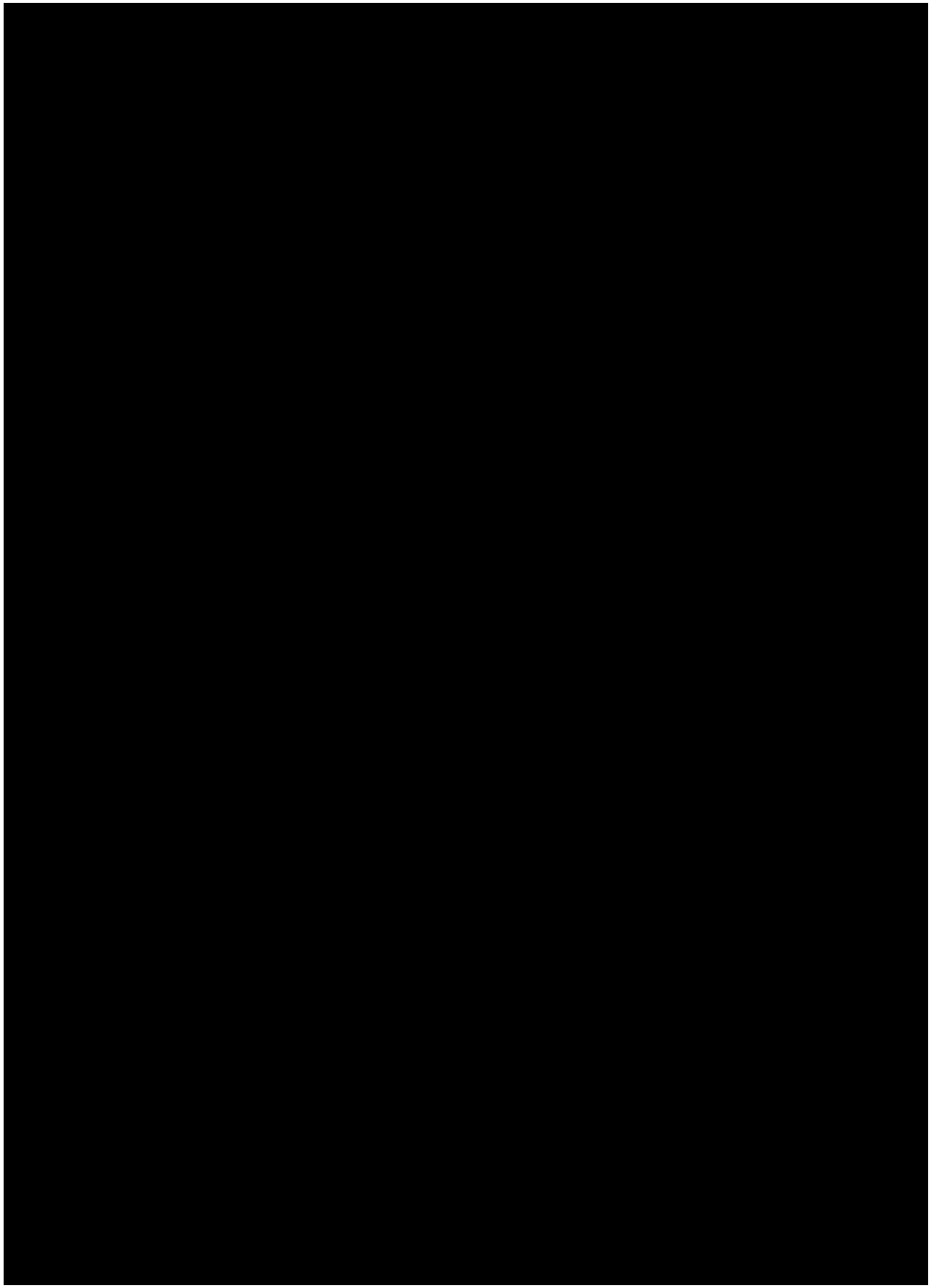
Inflammatory lesions, including abscesses, nodules, draining fistulae, total fistulae and other lesions will be counted by area.

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
- *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.







[redacted]

8.3.12 Subject's lesion count

This is a self-reported subject's assessed count of existing and new lesions in the HS affected areas. The subject's lesion count will be entered on the eDiary on a monthly basis and will be assessed at each office visit.

8.3.13 Loss of Response

Loss of response (LOR) is defined as a 50% or greater increase in the abscess and/or inflammatory nodule (AN) count at a regular or unscheduled visit compared to the average AN count from the 3 previous visits (including core visits) or the Week 52 visit, whichever is lower, and the increase is at least 3 AN.

If at a regular or extra visit, the subject experiences a 30% or greater increase in AN count compared to the average AN count from 3 previous visits (including core visits) or the Week 52 visit, whichever is lower, with an increase of at least 2 AN the subject should be reassessed within 2-4 weeks. A further increase in the AN count of at least 2 AN would confirm disease progression and be considered a LOR.

[redacted]

8.3.15 Appropriateness of efficacy assessments

HiSCR at Week 16 is a primary endpoint assessed in core studies. It was developed and validated as part of the development program of adalimumab in HS. The primary endpoint of the extension study is using consequently the same variables as used in the core studies and is defined as cumulative rate of subjects who were HiSCR responders at Week 52 in the core studies and have a loss of response by Week 104 following the randomized withdrawal period.

[redacted]

[redacted]

8.4 Safety

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

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 8 weeks if on blinded treatment or 12 weeks if on open label treatment, or more frequently if needed) for safety monitoring and discussion of the subject´s health status until the subject can again visit the site.

Significant events (e.g. AE, infection) should be entered in the eCRF as appropriate.

If subjects cannot visit the site to have blood/urine samples drawn for central laboratory analysis, performing the safety laboratory tests locally, e.g. by the subject´s general practitioner, could be allowed as appropriate.

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 can 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.

Alternatively, depending on local regulations and capabilities, study site staff may visit the subject at home to draw blood/ urine samples if needed.

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

Table 8-6 Assessments and Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological system will be performed as indicated in Table 8-1. If indicated 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 study site staff throughout the study. Information for all physical examinations must be included in the source documentation at the study site. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

Assessment	Specification
Vital signs	Vital signs including BP and pulse measurements will be assessed at every scheduled on-site 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 (measurement 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.
Weight	Body weight will be measured as indicated in Table 8-1. 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 Week 52 visit will be used to stratify the subject population for randomization.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed below, unless noted otherwise. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the Laboratory Manual. Refer to the Laboratory Manual for identification of laboratory reference range values and the schema for notification of site staff and Novartis for out of range values. Clinically notable laboratory values are defined in 16.1 Appendix 1. 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.

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.

Table 8-7 Parameters evaluated as part of laboratory evaluations

Test Category	Test Name
Hematology	Hemoglobin, Hematocrit, Red blood cells, Platelets, White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils including band) will be measured at scheduled visits as specified in Table 8-1.

Test Category	Test Name
Clinical Chemistry	Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Bicarbonate, Calcium, Creatinine, Glucose, Magnesium, Phosphorus, Sodium, Potassium, Total Bilirubin, Total Protein, Urea, Uric Acid.
Pregnancy Test	Urine pregnancy test (refer to 'Pregnancy and assessments of fertility', Section 8.4.3).
Additional tests	High sensitivity C-reactive protein (part of clinical chemistry assessments).

8.4.2 Electrocardiogram (ECG)

Not Applicable.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

A local urine pregnancy test must be performed at Week 52 visit before randomization. A woman may be randomized based upon the local urine test result. A serum pregnancy test must be performed if the urine test is positive. Any woman with a positive serum pregnancy test result is not eligible for the trial and must be discontinued and followed. 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 study treatment.

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing 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. Refer to Table 8-1 for schedule of assessment.

8.4.4 Other safety evaluations

8.4.5 Appropriateness of safety measurements

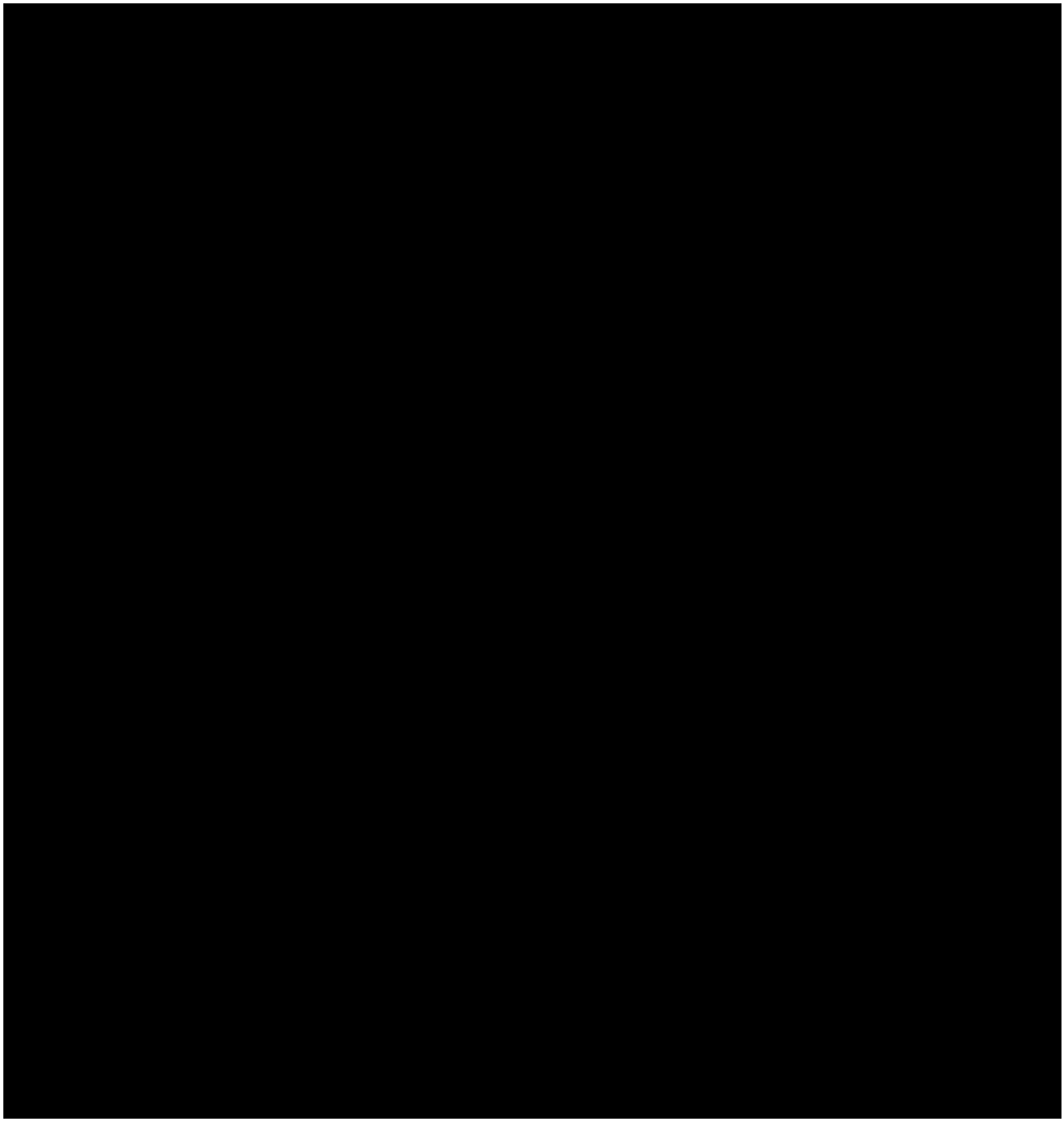
The safety assessments selected are reliable and standard for a biologic immunomodulating agent in HS.

8.5 Additional assessments

[redacted]

[redacted]

[redacted]



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 out-subject visits, in-subject 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.

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/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the subject
- Following emergency unblinding
- Emergence of the following adverse events: any adverse events that in the judgement 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 judgement 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.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent, Section 9.1.2). **Where possible, they should return for the assessments indicated** in the Assessment Schedule (Table 8-1). If the subject does not wish to attend any further visits, the subject should be asked to return to the site after discontinuation of study drug, for an End of Treatment (EoT) visit Week 104 (EoT-1) or Week 260 (EoT-2) and Follow-up visit Week 268/ F8.

Subjects who prematurely discontinue study treatment before Week 104 and do not wish to enter the post-treatment follow-up period, should be asked to return to the site for the Week 104 EoT-1 visit. Subjects who prematurely discontinue or complete open-label treatment after the Week 104 dose and do not wish to enter the post-treatment follow-up period, should be asked to return to the site for the Week 260 EoT-2 visit.

Assessments detailed in the EOT (EoT-1 or EoT-2) and Follow-up visit (Week 268/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 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 allow further collection of personal data

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

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

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

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

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

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

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

9.1.3 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 104 (EoT-1) or Week 260 (EoT-2) or visit at Follow-up Week 268 /F8). The Study Completion visit for individual subject will be defined as:

- Follow-up Week 268 /F8 visit for subjects who complete the post-treatment follow-up period
- Week 104 EoT-1 visit for subjects who prematurely discontinue study treatment before Week 104 and do not wish to enter post-treatment follow-up period or withdrew informed consent.
- Week 260 EoT-2 visit for HiSCR responder subjects at Week 52 who prematurely discontinue or complete open-label treatment after Week 104 dose and do not wish to enter post-treatment follow-up period or withdrew informed consent. Or for HiSCR non-responder subject at Week 52 who prematurely discontinue or complete open-label treatment and do not wish to enter post-treatment follow-up period or withdrew informed consent.

The investigator must provide follow-up medical care for all subjects who are pre-maturely withdrawn from the 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 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 by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject.
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a serious adverse event (SAE - see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. action taken regarding with study treatment.

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

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

6. concomitant medication or non-drug therapy given
7. its outcome
    - not recovered/not resolved
    - recovered/resolved
    - recovered/resolved with sequelae
    - fatal
    - unknown

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

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

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

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

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

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

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

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

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

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 Subject Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (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 investigator's participating in the study. The DMC will assess data from the interim analysis of the core studies, as well as the progress of a clinical trial of core studies and extension study safety data and critical efficacy variables, and it will recommend to the sponsor whether to continue, modify or terminate the 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) was established for the entire Hidradenitis Suppurativa development program comprising disease area experts, investigators participating in the trial, i.e. not being members of the DMC and Novartis representatives from the CTT.

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 Electronic Data Capture (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).

[redacted] 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).

Dates of randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by 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.

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

In the event of a global health crisis requiring social distancing or limited travel/attendance to site, remote site initiation and monitoring could be considered.

12 Data analysis and statistical methods

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 by randomization. According to the intention-to-treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure. Mis-randomized subjects (mis-randomized in IRT) will be excluded from FAS. Mis-randomized

subjects are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and no study medication was administered to the subject.

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

12.2 Subject demographics and other baseline characteristics

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.

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 secukinumab (300 mg q4w or 300 mg q2w) in subjects with moderate to severe HS who were HiSCR responders at Week 52 of the core studies, with respect to loss of response by Week 104, compared to placebo.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is time to loss of response (LOR) up to Week 104 in subjects who were HiSCR responders at Week 52 in the core studies. LOR is defined as a 50% increase in AN (abscess and/or nodules) at a regular or unscheduled visit compared to the average AN count from 3 previous visits or the Week 52, whichever is lower, and the increase was at least of 3 AN. The LOR will be considered also if at a regular or unscheduled visit, the subject had at least a 30% increase in AN count compared to the average count from the 3 previous visits or the Week 52, whichever is lower, with an increase of at least 2 AN, and if the subject had a further increase in AN count of at least 2 AN at a re-assessment within 2-4 weeks.

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 are that the hazard rate for loss of response up to Week 104 (randomized withdrawal period) in subjects who were HiSCR responders at Week 52 in the core studies is greater or not different in the secukinumab 300 mg q2w group compared to the corresponding placebo group as well as in the secukinumab 300mg q4w group compared to the corresponding placebo group.

Let us assume the following:

- λ_T^{q2w} denotes the hazard rate for loss of response in the secukinumab 300 mg q2w.
- λ_P^{q2w} denotes the hazard rate for loss of response in the placebo group (secukinumab 300 mg q2w in the core studies).
- λ_T^{q4w} denotes the hazard rate for loss of response in the secukinumab 300 mg q4w.
- λ_P^{q4w} denotes the hazard rate for loss of response in the placebo group (secukinumab 300 mg q4w in the core studies).

The following hypotheses will be tested

- H_{01}: $\frac{\lambda_T^{q2w}}{\lambda_P^{q2w}} \geq 1$ versus H_{A1}: $\frac{\lambda_T^{q2w}}{\lambda_P^{q2w}} < 1$,
- H_{02}: $\frac{\lambda_T^{q4w}}{\lambda_P^{q4w}} \geq 1$ versus H_{A2}: $\frac{\lambda_T^{q4w}}{\lambda_P^{q4w}} < 1$

In other words

- H_{01}: The hazard rate of loss of response up to Week 104 is greater or equal in the Secukinumab 300 mg q2w group relative to the placebo group.
- H_{02}: The hazard rate of loss of response up to Week 104 is greater or equal in the Secukinumab 300 mg q4w group relative to the placebo group.

Number and percentage of subjects experienced loss of response based on the number of subjects in the full analysis set at risk as denominator will be provided by treatment group.

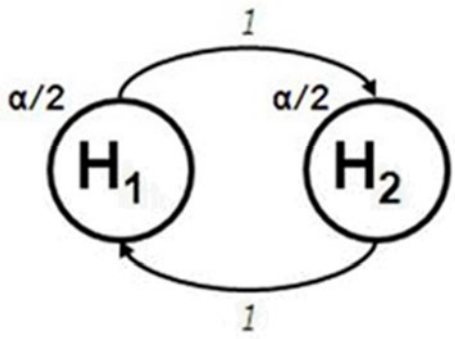
For loss of response, between-treatment differences will be evaluated using a log-rank test, stratified by region and body weight stratum, to compare the survival functions between secukinumab treatment groups versus placebo. The hazard ratios for these comparisons for loss of response and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model with treatment group and baseline AN counts of extension study as explanatory variable and stratified by region and body weight stratum.

Separate analyses will be performed for comparison of secukinumab 300 mg q2w with placebo and secukinumab 300 mg q4w with placebo. The two placebo groups will not be pooled for this analysis.

Testing strategy

The familywise error will be set to α=2.5% (one-sided). The two hypotheses H_{01} (referring to 300 mg q2w) and H_{02} (referring to 300 mg q4w) will be tested at $\alpha/2$=1.25% one-sided. In case, a null hypothesis has been rejected for one regimen, but not for the other regimen, the alpha can be shifted to the other regimen and the null hypotheses can be retested at level α=2.5% (one-sided). The graphical approach of Bretz et al (2009) for sequentially rejective testing procedures is used to illustrate the testing strategy (Figure 12-1):

Figure 12-1 Testing strategy



12.4.3 Handling of missing values/censoring/discontinuations

For the primary analysis, subjects who did not experience loss of response up to Week 104 or subjects who missed ≥2 consecutive assessments will be considered as censored. Censoring will also be applied to subjects who permanently discontinued study treatment. Placebo subjects who switched to secukinumab arm will be considered as loss of response at the date of switching. Secukinumab subjects who get up-titration will be considered as loss of response at the date of up-titration. Other time-to-event analyses will be handled analogously.

For other binary endpoints (HiSCR, [redacted]), missing data 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, i.e. "jump to reference" (J2R) assumption for the secukinumab arms, missing at random assumption for placebo arm (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 missing at random (MAR) assumption.

In case a higher than anticipated number of missing values would be observed in the core studies (CAIN457M2301 and CAIN457M2302), due to the COVID-19 global health crisis or potential similar outbreaks, the Sponsor may consider extending the recruitment in order to maintain the pre-defined statistical power. However, the number of additionally recruited patients in the core trials is not expected to be more than 15% of the initial sample size. Consequently, there might be an increased number of patients entering this extension study.

Furthermore, Novartis might consider additional sensitivity analyses to assess the potential impact of the COVID-19 pandemic, as well as any possible other global outbreak, on the study results.

12.4.4 Sensitivity and Supportive analyses

Supportive analysis 1

Subjects who did not experience loss of response up to Week 104 will be considered as censored. Censoring will also be applied to subjects who permanently discontinued study treatment. Subjects who have missed ≥2 consecutive assessments will not be considered as censored. If a loss of response is observed at the first assessment after ≥2 missed consecutive assessments, it is assumed that the first missing assessment is a loss of response. Otherwise it will be assumed that no LOR happened during the missed assessments. Placebo subjects who switched to secukinumab arm will be considered as loss of response at the date of switching. Secukinumab subjects who get up-titration will also be considered as loss of response at the date of up-titration.

Supportive analysis 2

Subjects who did not experience loss of response up to Week 104 will be considered as censored. Censoring will also be applied to subjects who missed ≥2 consecutive assessments. Subjects who permanently discontinued study treatment will be considered as loss of response. Placebo subjects who switched to secukinumab arm will be considered as loss of response at the date of switching. Secukinumab subjects who get up-titration will also be considered as loss of response at the date of up-titration.

Additionally, The Kaplan-Meier estimates of the (1 minus cumulative rate loss of response) for each treatment will be plotted. The plot will include the number of subjects at risk for each treatment group at pre-specified time points (e.g., visits).

The number of subjects with loss of response, number of subjects in the analysis set, estimate of cumulative rate up to Week 104, median event time, and its estimated standard error, as estimable will be provided for each treatment group. In addition, for pre-specified time intervals (e.g., 8-week intervals) the following will be presented:

- for each treatment group and time interval: subjects at risk, subjects with loss of response, subjects with loss of response divided by subjects at risk, cumulative subjects with event and cumulative event probability including 95% confidence interval.

12.5 Analysis of secondary endpoints

12.5.1 Safety endpoints

All safety evaluations will be performed on the Safety Set.

Analysis of adverse events will be based on treatment emergent events, which are defined as events started on or after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose +84 days.

Other safety variable will be evaluated based on on-treatment events, which are defined as any events that happened after first dose of study treatment and on or before last dose +84 days.

Safety analysis will be performed on actual treatment.

Adverse events

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

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

Vital signs

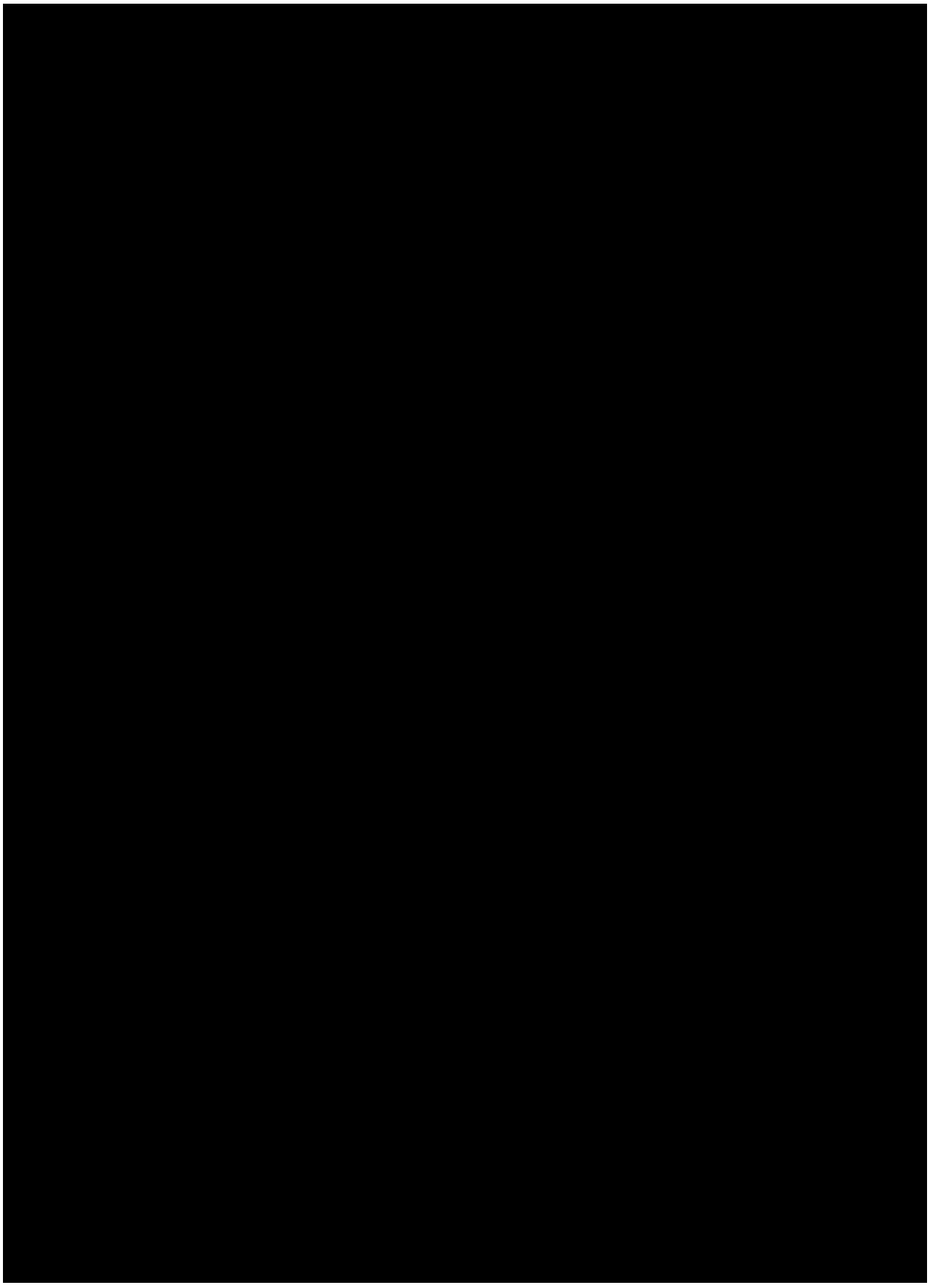
Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and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

Clinical laboratory evaluations

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

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.



12.7 Interim analyses

A PEA is planned to be performed when all subjects have completed the visit at which the primary endpoint is assessed (Week 104). After this analysis, the study will be open label.

All data collected up to Week 104 will be analyzed.

Additional interim analysis may be conducted at various time points for publications or health authority requests. The study procedures will not be modified as a result of these interim analyses.

12.8 Sample size calculation

In case of a global health crisis limiting the performance of assessments or the administration of drug, the number of evaluable subjects might be reduced due to missing data. In case the number of missing values considerably affects the statistical power (see Section 12.4.3), the Sponsor may consider extending the recruitment of subjects in the core studies (CAIN457M2301 and CAIN457M2302), As a consequence, an increased number of subjects could roll over into the extension study as well, and, thus, the number of included subjects in this extension study could be increased.

12.8.1 Primary endpoint(s)

Assumptions for the number of subjects eligible for entering randomized withdrawal:

- Drop-out rate up to Week 52 in core studies: 21%
- HiSCR response rate at Week 52 on secukinumab 300 mg q2w in core studies: 45%. Same for secukinumab 300 mg q4w.
- Type-I-error rate is defined to one-sided 2.5%
- Drop-out rate from Week 52 to Week 104: 20%

With these assumptions it is estimated to have 168 subjects eligible per regimen to enter the randomized withdrawal, with a randomization ratio of 2:1 this would be 112 subjects on

secukinumab regimen and 56 subjects on placebo. If we assume 25% of the subjects in secukinumab arm and 50% in placebo arm would experience loss of response by Week 76 (from Humira data), with about 160 subjects the study would have more than 85% power to detect a difference. The sample power calculation was done in East 6.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonisation (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 subject last visit*) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.) .

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

13.4 Quality Control and Quality Assurance

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

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

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

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.

15 References

References are available upon request

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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: > 2.5 x ULN

Renal Function

Creatinine (serum): > 1.5 x ULN

Hematology

Hemoglobin: ≥ 20 g/dl decrease

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

16.2 Appendix 2: Blood samples collection

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

		Hematology	Clinical Chemistry	[redacted]	
	Visit Name	Volume (ml)	Volume (ml)		Total Volume (ml)
Randomized Withdrawal Period	Week 52*				
	Week 60	4.8	3.5		8.3
	Week 68	4.8	3.5		8.3
	Week 76	4.8	3.5		8.3
	Week 84	4.8	3.5		8.3
	Week 92	4.8	3.5		8.3
	Week 100	4.8	3.5		8.3
	LOR visit or Week 104/EOT-1**	4.8	3.5		25.3
Open-label Period	Week 108	4.8	3.5		8.3
	Week 120	4.8	3.5		8.3
	Week 132	4.8	3.5		8.3
	Week 144	4.8	3.5		8.3
	Week 156	4.8	3.5		8.3
	Week 168	4.8	3.5		8.3
	Week 180	4.8	3.5		8.3
	Week 192	4.8	3.5		8.3
	Week 204	4.8	3.5		8.3
	Week 216	4.8	3.5		8.3
	Week 228	4.8	3.5		8.3
	Week 240	4.8	3.5		8.3
	Week 252	4.8	3.5		8.3
	Week 260/EOT-2	4.8	3.5		8.3
	Week 268/ follow-up	4.8	3.5		8.3

* Wk 52 samples will be collected as a core trial (AIN457M2301/AIN457M2302) procedure

** Subject will have either a Week 104/EOT-1 visit or a LOR visit if LOR occurs prior to Week 104