NOVARTIS

US Clinical Development and Medical Affairs - General Medicine

AIN457/Secukinumab

Clinical Trial Protocol CAIN457AUS07 / NCT03055494

A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to explore changes in subcutaneous adipose tissue and modulation of skin inflammation after 12 weeks of treatment with secukinumab, compared to placebo, and up to 52 weeks of treatment with secukinumab in adult patients with moderate to severe plaque psoriasis (ObePso-S)

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[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

List of tables

[redacted]

List of figures

[redacted]

List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
CD	Cluster of differentiation
CDER	Center for Drug Evaluation and Research
CFR	US Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
(e)CRF	(electronic) Case Report/Record Form
CRO	Contract Research Organization
CS	Corticosteroids
CSR	Clinical Study Report
CT	Computerized tomography
CTRD	Clinical Trial Results Database
CVD	Cardiovascular disease
DS&E	Drug Safety & Epidemiology
DSM	Drug Supply Management
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	End of treatment
EU	European Union
FACS	Fluorescence-activated cell sorting
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidatse
Hb	Hemoglobin
HIV	Human immunodeficiency virus
hs-CRP	high sensitivity C-reactive protein
HOMA-IR	Homeostatic model assessment-insulin resistance
IB	Investigator's Brochure
ICAM	Intercellular adhesion molecule
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for Use
IGA mod 2011	Investigator's Global Assessment modified 2011
IL	Interleukin
IUD	Intrauterine device
i.v.	Intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LS	Lesional

[redacted]

MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
[redacted]	[redacted]
MTX	Methotrexate
[redacted]	[redacted]
OTC	Over-the-counter
PASI	Psoriasis Area and Severity Index
PC	Personal Computer
PET	Positron Emission Tomography
PMDA	Pharmaceuticals and Medical Devices Agency
PPD	Purified protein derivative
PUVA	Psoralen ultraviolet A
OC/RDC	Oracle Clinical/Remote Data Capture
PET	Positron emission tomography
PFS	Pre-filled syringe
RT-PCR	Reverse transcription - polymerase chain reaction
SAE	Serious Adverse Event
s.c.	Subcutaneous
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvate transaminase
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TCS	Topical corticosteroids
TD	Study Treatment Discontinuation
TH17	T-helper 17 (cells)
TNF	Tumor necrosis factor
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
VCAM	Vascular cell adhesion molecule
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Control drug	Drugs(s) 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 patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Investigational drug	The 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.”
Medication number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient ID	A unique number assigned to each patient upon signing the informed consent
Period	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper.
Study drug/treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Amendment 2

Amendment rationale

The primary purpose of this amendment is to allow for the enrollment of healthy volunteers at [redacted] to act as a control cohort for the purpose of comparing skin, adipose tissue, [redacted] data/outcomes to the psoriasis patients enrolled in the study.

Additionally, text related to eSource was deleted as it was not used in this study.

At the time of this amendment, all psoriasis patients have been enrolled in the study.

Changes to the protocol

- List of abbreviations and Glossary of terms was updated to remove eSource
- Section 3.1.6 was added for the control cohort of healthy volunteers
- Table 6-2 Assessment schedule for healthy control cohort was added
- Section 8 and Section 8.1 were updated to remove reference to eSource
- Section 8.2 was updated to clarify that the data collection process is the same for the control cohort of healthy volunteers as for the psoriasis patients
- Section 9.6 was updated to clarify responsibility for certain data analyses and to specify where those analyses will be reported

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

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

[redacted]

Protocol summary

Protocol number	CAIN457AUS07
Full Title	A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to explore changes in subcutaneous adipose tissue and modulation of skin inflammation after 12 weeks of treatment with secukinumab, compared to placebo, and up to 52 weeks of treatment with secukinumab in adult patients with moderate to severe plaque psoriasis (ObePso-S)
Brief title	Study to explore the effect of secukinumab, compared to placebo, on fat tissue and skin in plaque psoriasis patients
Sponsor and Clinical Phase	Novartis Pharmaceuticals Corporation Phase 4
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Secukinumab targets interleukin 17a (IL-17a) which may play a critical role in the pathophysiology of psoriasis. IL-17 is not established as a factor in excess adiposity, however reports suggest that obesity may be a driver for the formation of TH17 T-cells. This study will provide a comparison of secukinumab to placebo with respect to skin inflammation as measured by skin exams in comparison to skin biopsies, adipose tissue and blood sample analyses.
Primary Objective(s)	The primary objective of this study is to explore the modulation of subcutaneous adipose tissue and skin inflammation from baseline to Week 12 in patients with moderate to severe plaque psoriasis treated with secukinumab compared to placebo
Secondary Objectives	• To explore changes in biometric measurements from baseline to Week 12 in patients with moderate to severe plaque psoriasis treated with secukinumab compared to placebo • To explore the modulation of subcutaneous adipose tissue and skin inflammation from baseline to Week 52 in patients with moderate to severe plaque psoriasis treated with secukinumab
[redacted]	
Study design	This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study in approximately 75 patients with moderate to severe chronic plaque psoriasis.

[redacted]

	The patients will be enrolled from approximately 15 sites within the United States. The study consists five of periods: screening (from 1-4 weeks); a double-blind treatment period (12 weeks); a double-blind induction period (4 weeks); an open-label treatment period (36 weeks); and a follow-up period (1 week). The total study duration is up to 57 weeks. At the start of the double-blind treatment period, patients are randomized in a 2:1 ratio to one of two treatment groups – secukinumab or placebo. Randomization will be stratified by baseline body weight (<90 kg or ≥90 kg). At the end of the double-blind treatment period, all patients randomized to receive placebo will be switched to secukinumab treatment for the remainder of the study. Lesional (LS) [redacted] will be obtained via 6 mm punch biopsy from all patients at three time points: Baseline, Week 12, and Week 52.
Population	The study population will consist of approximately 75 male and female patients at least 18 years of age with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Key Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed 2. Males and females ≥18 years of age at the time of screening 3. Clinical diagnosis of chronic plaque-type psoriasis at least 6 months prior to randomization as determined by patient interview of his/her medical history and by confirmation of diagnosis through physical examination by the investigator 4. Moderate to severe plaque psoriasis as defined at baseline by: o ≥10% Body Surface Area (BSA) involvement and o PASI total score of ≥12 and o IGA mod 2011 score of ≥3 (based on a scale of 0-4) 5. Candidate for systemic therapy, defined as having psoriasis inadequately controlled by: o Topical treatment (including topical corticosteroids) and/or o Phototherapy and/or o Previous systemic therapy
Key Exclusion criteria	• Forms of psoriasis other than chronic plaque psoriasis • Medication-induced or medication exacerbated psoriasis • Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17RA receptors • Diagnosis of other active ongoing skin diseases or skin infections (bacterial, fungal, or viral), or inflammatory diseases other than psoriasis that may interfere with the evaluation of psoriasis • History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection • Positive serology for human immunodeficiency virus (HIV), hepatitis B or C infection • Pregnant or nursing (lactating) women

[redacted]

Study treatment	Study drug: • Secukinumab 150 mg: 1 ml liquid formulation in a single-use prefilled syringe (PFS) for subcutaneous injection Control drug: • Placebo to secukinumab 150 mg: 1 ml liquid formulation in a single-use prefilled syringe (PFS) for subcutaneous injection
Efficacy assessments	• Modulation of subcutaneous adipose tissue and skin inflammation [redacted] • PASI: Psoriasis Area and Severity Index [redacted]
Key safety assessments	• Adverse events and serious adverse events • Laboratory assessments (e.g., hematology, clinical chemistry, hs-CRP, HbA1c, HOMA-IR, viral serology, serum and urine pregnancy) • Vital signs, weight, waist circumference, BMI, physical examination
Data analysis	A designated Contract Research Organization will perform the statistical analysis. It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of patients will be available for analysis. The analysis will be conducted on all patient data at the end of Week 12, and at the time the trial ends at Week 53. The following analysis sets will be used for the statistical reporting and analyses: Randomized Set: The Randomized Set includes all randomized patients. Safety Set: The Safety Set includes all patients who received at least one dose of study medication. Patients will be included in the analysis according to treatment received. Full Analysis Set: The Full Analysis Set comprises all patients to whom study medication has been assigned. Patients inappropriately randomized (e.g., IRT was called in error for randomization of a screen failed patient) will be excluded from this analysis set. Data will be summarized by stratum with respect to demographic and baseline characteristics of all patients for the Randomized Set and the Full Analysis Set. Concomitant medications will be summarized by treatment using frequency counts and percentages for the Safety Set. Efficacy, safety, and other data will be summarized for all weeks up to Week 53. Response of psoriasis skin lesions to treatment as measured by: a. Response in skin histology/K16 expression to treatment (yes, no) b. PASI 90 (yes, no) The primary analysis time point will be at Week 12. For the two primary efficacy variables at each time point (response in skin histology/K16 expression to treatment at Week 12, PASI 90 at Weeks 4, 8, and 12), 95% confidence intervals for the difference between the two treatment groups with

[redacted]

respect to the percentage of patients who have the "event" will be calculated using the normal approximation to the binomial distribution.

For the two primary efficacy variables at Week 12 (and other time points), a patient with a missing assessment will be considered as a non-responder.

The analysis of the primary efficacy variables will be based on the Full Analysis Set.

Cross-classification tables of response in skin histology/K16 expression to treatment (yes, no) [redacted] In addition, to assess the association between skin histology/K16 expression results [redacted], a logistic regression analysis will be performed and the odds ratio and 95% confidence interval for the odds ratio based on the fitted model will be reported. The model will include response in skin histology/K16 expression as the response variable and treatment, body weight (<90 kg, ≥90 kg), [redacted]

The assessment of safety will be based mainly on the frequency of adverse events and laboratory data. Other safety data, including vital signs (weight, blood pressure, waist circumference, BMI), and clinical laboratory variables (glucose, insulin, hs-CRP, HOMA-IR, HbA1c) will be summarized by stratum, as appropriate.

Analysis of safety data will be based on the Safety Set.

The table below considers total sample sizes of 75 patients (50 in secukinumab group and 25 in placebo group) and 99 patients (66 in secukinumab group and 33 in placebo group) to estimate the difference between the two groups with respect to the pooled estimate of the two percentages of patients who have the "event" at Week 12 for each of the two primary efficacy variables. The entries in the table are the "margin of error" (half-width of confidence interval) for a two-sided 95% confidence interval (Julious and Patterson, 2004; Kianifard and Islam, 2011; nQuery Advisor 7.0).

Percentage with "event"	Half-width of confidence interval for n = 75	Half-width of confidence interval for n = 99
30%	25.0%	21.4%
40%	26.5%	22.7%
50%	27.0%	23.2%
60%	26.5%	22.7%
70%	25.0%	21.4%

Based on the results in the above table, it was decided that approximately 75 randomized patients (50 in secukinumab group and 25 in placebo group) will be randomized in this [redacted] study to estimate the difference in response rates between the two treatment groups.

Key words	Plaque psoriasis, secukinumab, biologic, monoclonal antibody, adipose tissue, skin inflammation

[redacted]

1 Introduction

1.1 Background

Psoriasis vulgaris is best conceptualized as a disease of focal cutaneous inflammation, but with associated systemic inflammation that likely results from effects of circulating cytokines and other inflammatory molecules that are produced at excess levels in skin lesions and diffuse into the circulation. IL-17 and tumor necrosis factor (TNF) are consistently increased in plasma of untreated patients with moderate-to-severe psoriasis and these are decreased following skin improvements with a number of biologic treatments, e.g., IL-23 inhibitors or TNF inhibitors (Chiricozzi et al 2011).

Consequences of cytokine-driven system inflammation include: 1) activation of a set of genes and proteins in circulating leukocytes that increase inflammatory potential and would enable migration into various tissues according to chemokine gradients that may be set up; 2) vascular inflammation associated with large vessels as demonstrated by PET-CT imaging in past studies; 3) an increase in cardiovascular disease (CVD) risk; 4) inflammation in adipose tissue with the consequence of increased resistance to insulin signaling and metabolic syndrome or diabetes; and 5) inflammation in other tissues such as the gut or joints that may drive increased incidence of inflammatory bowel disease or psoriatic arthritis, respectively (Davidovici et al 2010).

Psoriasis is also associated with overt obesity in a large fraction of patients. While IL-17 is not established as a factor in the formation of excess adiposity, there are reports that suggest obesity may be a driver for the formation of Th17 T-cells (Endo et al 2015; Luczyński et al 2015; Reis et al 2015). Additionally, treatment of patients with TNF antagonists can lead to significant weight gain, a finding that worsens the obesity problem and which mechanistically makes sense with inhibition of TNF signaling (Tan et al 2013; Renzo et al 2011; Gisondi et al 2008; Saraceno et al 2008).

Therapeutic agents with different mechanisms, e.g., secukinumab, would not be expected to produce this negative effect of weight gain. The metabolic and inflammatory effects of IL-17 signaling in adipose tissue are not well understood at present, but use of a directed IL-17 antagonist has the potential to define the physiological effects of excess IL-17 signaling in this tissue compartment. Thus this study has the potential to establish non-negative effects (i.e., no weight gain) of secukinumab on adiposity, as well as pro-health consequences of blocking IL-17 in psoriasis patients.

The present study has the dual goals of examining anti-inflammatory effects of secukinumab on two "systemic" tissues that lead to co-morbidity: the vascular compartment and subcutaneous adipose tissue. In both cases, treatment benefits would be related to reductions in inflammation in psoriasis vulgaris skin lesions. Elements of the vascular compartment that affect cardiovascular disease that will be studied include endothelial cells (via microparticles), circulating leukocytes (via microparticle and full cell analysis), and inflammatory/cardiovascular risk proteins in blood plasma (Ho et al 2016). Elements of the adipose tissue response include the study of overall adiposity (e.g., weight, BMI).

[redacted]

Ongoing studies are using PET-CT or PET-MRI to visualize inflammation in large vessels during secukinumab treatment, but this imaging is based on metabolic activity of macrophages that are resident within the sub-endothelial space of large vessels and macrophage infiltration of any tissue may be relatively fixed and non-reversible, even with strong anti-inflammatory treatments (Mehta et al 2011; Naik et al 2015). Researchers at [redacted] have found that aortic endothelial cells respond to the combination of TNF and IL-17 by synthesis of fractalkine, which is a chemotactic chemokine for "inflammatory' macrophages that are associated with atherosclerosis formation. Macrophages with this phenotype have been identified in blood of psoriasis patients. The effects of high levels of IL-17, TNF, and leukocyte trafficking across aortic endothelium will set-up increased microparticles (apoptotic bodies) derived from these endothelial cells in the blood. A beneficial effect of IL-17 blockade on aortic inflammation can thus be measured by quantification of endothelial cell derived microparticles as well as expression of cytokine-induced proteins, e.g., adhesion molecules such as ICAM-1 and VCAM, in these particles using flow-cytometry with appropriate antibodies to quantify levels of protein expression.

In a recent study of IL-17 inhibition with ixekizumab, researchers at [redacted] were able to demonstrate that a set of IL-17 induced adhesion molecules on blood monocytes were reduced at the level of gene expression within two weeks of starting this antibody (Wang et al 2014). The current proposal would extend this analysis to include measuring expression of cognate surface proteins on circulating leukocytes, including inflammatory macrophages, and the integration of this data with expression of cytokine-induced proteins on microparticles derived from endothelial cells and leukocytes.

Finally, a recent study has found that there was increased expression of IL-17 signaling pathways in non-lesional skin of psoriasis patients (Chiricozzi et al 2016). As a feature of this protocol, we would correlate anti-inflammatory effects of secukinumab in "internal" sites of endothelium, blood leukocytes, [redacted] after treatment to test this hypothesis. If the concept is validated, it could have tremendous benefit for the design of future studies designed to prove "distant" effects of inflammatory cytokines in psoriasis patients on peripheral tissues.

1.2 Purpose

Obesity has been linked to poorer long-term outcome in patients with psoriasis, with some evidence that weight loss may improve psoriasis (Higa-Sansone et al 2004; Naldi et al 2005; Wolters 2005). In addition, one recent study showed that moderate weight loss may supplement pharmacologic treatment (Giscondi et al 2008). However, what is unclear is if inflammatory cytokines upregulated in psoriasis patients by the TH-17 pathway are also contributing to the production of adipose tissue in these patients, and thereby also affecting the mechanism of insulin resistance. These factors may contribute to the higher association of complications from insulin resistance such as dyslipidemia, hypertension, and premature heart disease in psoriasis patients. Patients with moderate to severe psoriasis who undergo anti-IL-17A treatment with secukinumab that improves the skin manifestations of psoriasis but its effect on adipose tissue are also of intense clinical and scientific interest.

[redacted]

The purpose of this study is to explore changes in subcutaneous adipose tissue and skin inflammation in patients with moderate to severe plaque psoriasis treated with secukinumab 300 mg compared to placebo at Week 12.

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • To explore the modulation of subcutaneous adipose tissue and skin inflammation from baseline to Week 12 in patients with moderate to severe plaque psoriasis treated with secukinumab compared to placebo	**Endpoint(s) for primary objective(s)** • Response of psoriasis skin lesions to treatment as measured by: a. Response in skin histology/K16 expression to treatment (yes, no) b. PASI 90 (yes, no)
Secondary Objective(s) • To explore changes in biometric measurements from baseline to Week 12 in patients with moderate to severe plaque psoriasis treated with secukinumab compared to placebo	**Endpoint(s) for secondary objective(s)** • Vital signs (blood pressure, weight, waist circumference, BMI), clinical laboratory variables (glucose, insulin, hs-CRP, HOMA-IR, HbA1c)
• To explore the modulation of subcutaneous adipose tissue and skin inflammation from baseline to Week 52 in patients with moderate to severe plaque psoriasis treated with secukinumab	• Response of psoriasis skin lesions to treatment as measured by: a. Response in skin histology/K16 expression to treatment (yes, no) b. PASI 90 (yes, no)
[redacted]	

[redacted]

3 Investigational plan

3.1 Study design

This study uses a randomized, double-blind, placebo-controlled, parallel-group, multicenter design. Approximately 75 moderate to severe plaque psoriasis patients from approximately 15 sites will be randomized at Visit 2/Baseline in a 2:1 ratio to receive secukinumab 300 mg or placebo, respectively. Randomization will be stratified by body weight collected at Visit 2 (< 90 kg or ≥90 kg).

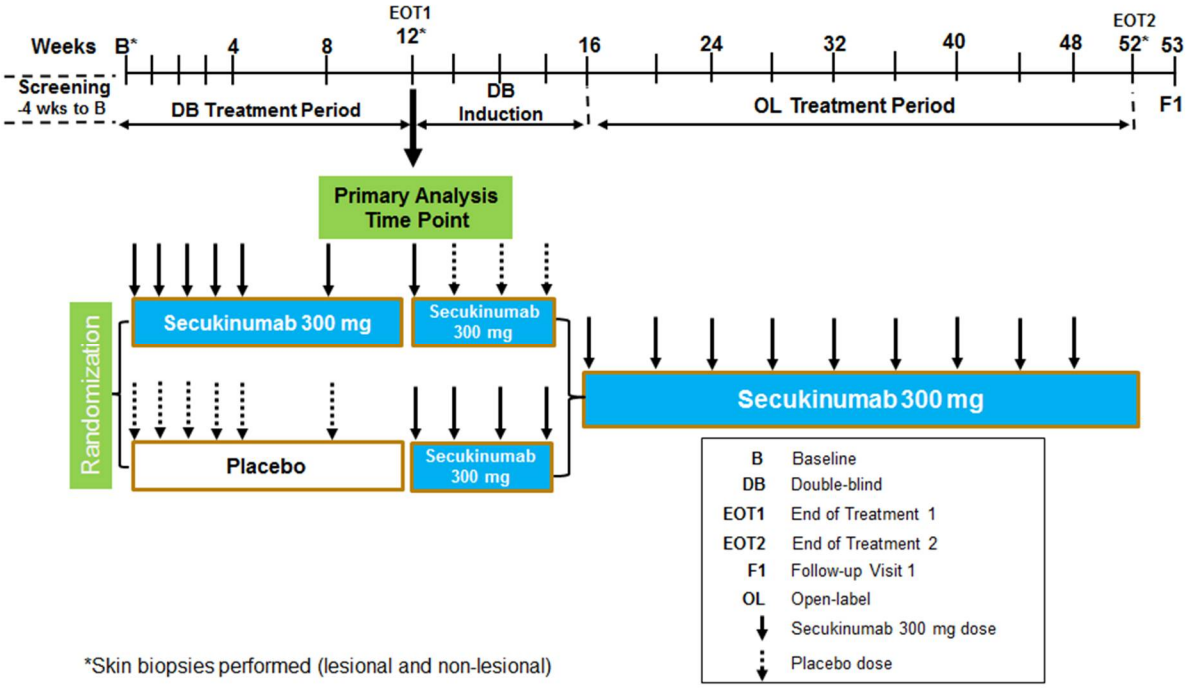
The study consists of five periods:

- Screening (from 1-4 weeks);
- Double-blind Treatment Period (12 weeks);
- Double-blind Induction Period (4 weeks);
- Open-label Treatment Period (36 weeks); and
- Follow-up Period (1 week).

A schematic of the study design is presented in Figure 3-1, while a detailed visit and assessment schedule can be found in Table 6-1. An interim analysis is planned after Week 12, which is the primary analysis time point for the study.

[redacted]

Figure 3-1 Study design



3.1.1 Screening period (Screening to randomization)

The duration of the screening period will be up to four weeks. Screening will be used to assess patient eligibility and to taper patients off prohibited medications and treatments.

3.1.2 Double-blind treatment period (Randomization to Week 12 pre-dose)

At the start of the Double-blind Treatment Period, eligible patients will be randomized via Interactive Response Technology (IRT) in a 2:1 ratio to one of two treatment arms (secukinumab 300 mg or placebo). Randomization will be stratified by body weight collected at Visit 2 (< 90 kg or ≥90 kg).

During this period, all patients will attend study visits at Baseline, Weeks 1, 2, 3, 4, 8 and 12, and all doses of study treatment will be self-administered at the study site.

[redacted]

Assessments for the primary efficacy variable will be performed at Week 12 prior to patients receiving their Week 12 dose.

All patients who discontinue from the study prematurely for any reason before the end of the Double-blind Treatment Period should return to the study site for the performance of the Visit 8/Week 12 End of Treatment (EOT1) assessments. This visit should be scheduled approximately four weeks after the last dose of study treatment.

[redacted]

3.1.3 Double-blind induction period (Week 12 dose through Week 15 dose)

All patients who complete the Double-blind Treatment Period will enter the Double-blind Induction Period. The Double-blind Induction Period is defined as the Week 12 dose through the Week 15 dose.

During this period, patients randomized to receive placebo at Visit 2/Baseline will be switched over to treatment with secukinumab 300 mg weekly for four weeks at Weeks 12, 13, 14, and 15.

Patients who were randomized to the secukinumab treatment group at Visit 2/Baseline will continue to self-administer secukinumab 300 mg at the Week 12 visit. In order to maintain the blind for the 12-week, placebo-controlled period, these patients will self-administer placebo injections at Weeks 13, 14, and 15.

Self-administration of the Weeks 12 and 13 doses will take place at the study site, while the doses at Weeks 14 and 15 will be self-administered at home.

All patients who discontinue from the study prematurely for any reason before the end of Double-blind Induction Period should return to the study site for the performance of the Visit 15/Week 52 End of Treatment (EOT2) assessments. This visit should be scheduled approximately four weeks after the last dose of study treatment.

3.1.4 Open-label treatment period (Week 16 to Week 52)

All patients who complete the Double-blind Induction Period will enter the Open-label Treatment Period. The Open-label Treatment Period is defined as Week 16 through Week 52.

All patients in this period will receive secukinumab 300 mg s.c. at four-week intervals beginning at Week 16 through Week 48 (last dose during the Open-Label Treatment Period).

Self-administration of the doses at Weeks 16, 24, 32, 40, and 48 will take place at the study site; the doses at Weeks 20, 28, 36, and 44 will be self-administered at home.

[redacted]

All patients who discontinue from the study prematurely for any reason before the end of the Open-label Treatment Period should return to the study site for the performance of the Visit 15/Week 52 (EOT2) assessments. This visit should be scheduled approximately four weeks after the last dose of study treatment.

3.1.5 Follow-up period visit 1 (F1)

All patients who undergo skin biopsies at Visit 15/Week 52 will return to the site approximately seven days later for Follow-up Visit 1 (F1) for suture removal and safety check.

Additionally, all patients who discontinue prematurely from the study and who undergo skin biopsies at their end of treatment visit (either Visit 8/Week 12 EOT1 or Visit 15/Week 52 EOT2) will return to the site approximately seven days later for Follow-up Visit 1 (F1) for suture removal and safety check.

[redacted]

3.1.6 Control cohort of healthy volunteers sub-study

Healthy volunteers will be enrolled at a single site ( ) to act as a control cohort for the purpose of comparing skin, adipose tissue, data/outcomes to the psoriasis patients enrolled in the study. Approximately 20 subjects without plaque psoriasis will be enrolled into the control cohort. These healthy volunteers will not receive study treatment.

Once all psoriasis patients have been randomized into the study, a listing of the requisite demographic and baseline characteristics (age, gender, weight, BMI) for the psoriasis study patients will be generated by Novartis from the clinical database and provided to The through an appropriate secure channel. This data is necessary for matched healthy volunteers to be recruited into the control cohort.

The control cohort will be enrolled while the 52-week treatment period for the psoriasis patients is ongoing; it is planned that the sample from the last healthy volunteer will be collected by the time the last psoriasis subject completes Week 52/EOT visit.

After signing informed consent, subjects in the control cohort will complete the assessments (including safety assessments) as indicated in Table 6-2. Visit 1 assessments may or may not occur on the same day.

During Visit 1, demographic and baseline characteristic data will be collected. Subjects will return to the site approximately 7 days following the Visit 1 biopsy for suture removal and safety check.

The analyses for the control cohort will be done in parallel with the psoriasis study patients, such that when the Week 52 data from the psoriasis patients is analyzed, the control data from the healthy volunteers will be available for comparison.

The control data and the psoriasis baseline and treatment data are best analyzed in a single batch and with a statistical model (a mixed effects model) that will consider group (control vs. disease), as well as treatment effects. The control data are needed to establish which baseline values of skin, fat, or blood measures are abnormal as a function of disease at baseline. This then provides the ability to determine if treatment with secukinumab normalizes baseline values or has effects to change inflammation that go beyond baseline disease characteristics. Without the control group, only a “drug effect” on the disease parameters could be computed without knowing whether what is modulated is part of pathogenic inflammation.

Inclusion criteria

Subjects in the control cohort will be judged by the investigator to be generally healthy, and will be generally matched to the age, gender, race, and weight/BMI composition of thepsoriasis study patients.

Exclusion criteria

Subjects fulfilling any of the following criteria are not eligible to enroll into the control cohort:

- Current use of immunosuppressive medications;
- Current use of anti-coagulant medications;
- Use of any investigational treatment within 4 weeks prior to study enrollment, or within a period of 5 half-lives of the investigational treatment prior to study enrollment, whichever is longer;
- Having a known autoimmune or inflammatory disease;
- History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to randomization;
- Pregnant or nursing (lactating) women.

3.2 Rationale for study design

The randomized, double-blind, placebo-controlled design used in this study is aligned with the Phase III trials of secukinumab, and with previous studies performed in the indication of chronic plaque psoriasis, and is in accordance with health authority guidelines and feedback, including the United States Food and Drug Administration (FDA).

The study population consists of adult patients with moderate to severe plaque-type psoriasis who are candidates for systemic therapy or phototherapy.

The primary analysis time point of the trial is at Week 12. This is in line with the timing of the primary analysis time point in the secukinumab Phase III trials, and will allow for assessment of efficacy at a point in time for which efficacy data from currently approved biologic therapies are available. Additionally, it is unknown if modulation of adipose tissue by secukinumab will be detectable by the primary time point of 12 weeks. The study design provides for treatment a duration of 52 weeks, which will allow for the assessment of longer-term effects of secukinumab in adipose tissue. For patients randomized to receive placebo at Visit 2/Baseline, the 52-week treatment duration allows these patients the opportunity to receive up to 40 weeks of treatment with secukinumab.

The study population will be described in more detail in Section 4 below.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The proposal to use a dose of secukinumab 300 mg administered with a weekly induction regimen for five weeks (at Randomization, Weeks 1, 2, 3, and 4) followed by treatment every four weeks thereafter (starting at Week 8) is in accordance with the current FDA-approved product labeling.

3.4 Rationale for choice of comparator

Due to the nature of psoriasis and the outcome measures used for this indication, a placebo arm is necessary to obtain reliable efficacy measurements. Moreover, the inclusion of a

[redacted]

placebo group is in accordance with health authority guidelines and feedback (CHMP Psoriasis Guideline-CHMP/EWP/2454/02 2004). The continuation of the placebo group up to the primary analysis time point at Week 12 is in the study design for the indication of chronic plaque-type psoriasis and is accepted by health authorities including the FDA, EMA and PMDA.

3.5 Purpose and timing of interim analyses/design adaptations

The primary analysis at Week 12 is considered an interim analysis and will be performed after all patients have completed the Week 12 visit and the database is locked. As Week 12 is the primary analysis time point, no adjustment to the significance level of 0.05 will be made. See Section 5.4 on treatment blinding for additional information.

For the purpose of developing a potential sub-study, the summary of patient demographic and baseline characteristics may be used.

3.6 Risks and benefits

Secukinumab is currently approved in the United States for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

The potential benefits of secukinumab treatment are detailed in Section 3.6.1.

The risk to patients in this trial will be minimized by compliance with the eligibility criteria and close clinical monitoring.

[redacted] Specifically, there is the risk of infection, bleeding and potentially unsatisfactory cosmetic results, e.g., due to scarring. A skin scar is expected after each biopsy procedure.

All quality, non-clinical pharmacology and toxicology data, as well as the available clinical efficacy and safety data for secukinumab are considered sufficient to expect a positive benefit/risk ratio for the treatment of moderate to severe psoriasis with secukinumab.

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

3.6.1 Clinical trials experience in plaque psoriasis

Four multicenter, randomized, double-blind, placebo-controlled trials (Trials 1, 2, 3, and 4) enrolled 2403 subjects (691 randomized to secukinumab 300 mg, 692 to secukinumab 150 mg, 694 to placebo, and 323 to a biologic active control) 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score greater than or equal to 12, an Investigator Global Assessment modified 2011 (IGA) of at least 3, and who were candidates for phototherapy or systemic therapy.

- Trial 1 enrolled 738 subjects (245 randomized to secukinumab 300 mg, 245 to secukinumab 150 mg, and 248 to placebo). Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks. Subjects randomized to

[redacted]

secukinumab received 300 mg or 150 mg doses at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks. Subjects randomized to receive placebo that were non-responders at Week 12 were then crossed over to receive secukinumab (either 300 mg or 150 mg) at Weeks 12, 13, 14, 15, and 16 followed by the same dose every 4 weeks. All subjects were followed for up to 52 weeks following first administration of study treatment.

- Trial 2 enrolled 1306 subjects (327 randomized to secukinumab 300 mg, 327 to secukinumab 150 mg, 326 to placebo and 323 to a biologic active control). Secukinumab and placebo data are described. Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks. Subjects randomized to secukinumab received 300 mg or 150 mg doses at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks. Subjects randomized to receive placebo that were non-responders at Week 12 then crossed over to receive secukinumab (either 300 mg or 150 mg) at Weeks 12, 13, 14, 15, and 16 followed by the same dose every 4 weeks. All subjects were followed for up to 52 weeks following first administration of study treatment.
- Trial 3 enrolled 177 subjects (59 randomized to secukinumab 300 mg, 59 to secukinumab 150 mg, and 59 to placebo) and assessed safety, tolerability, and usability of secukinumab self-administration via prefilled syringe for 12 weeks. Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks for up to 12 weeks total.
- Trial 4 enrolled 182 subjects (60 randomized to secukinumab 300 mg, 61 to secukinumab 150 mg, and 61 to placebo) and assessed safety, tolerability, and usability of secukinumab self-administration via Sensoready pen for 12 weeks. Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks for up to 12 weeks total.

In all trials, the co-primary efficacy variables were the proportion of subjects who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline to Week 12 and treatment success (clear or almost clear) on the Investigator's Global Assessment modified 2011 (IGA mod 2011). Other evaluated outcomes included the proportion of subjects who achieved a reduction in PASI score of at least 90% (PASI 90) from baseline at Week 12, maintenance of efficacy to Week 52, and improvements in itching, pain and scaling at Week 12 based on the Psoriasis Symptom Diary©.

The PASI is a composite score that takes into consideration both the percentage of body surface area affected and the nature and severity of psoriatic changes within the affected regions (induration, erythema and scaling). The IGA mod 2011 is a 5-category scale including "0 = clear" "1 = almost clear", "2 = mild", "3 = moderate" or "4 = severe" indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema and scaling. Treatment success of "clear" or "almost clear" consisted of no signs of psoriasis or normal to pink coloration of lesions, no thickening of the plaque and none to minimal focal scaling.

The results of Trials 1 - 4 are presented in Table 3-1.

[redacted]

Table 3-1 Clinical outcomes at Week 12 in adults with plaque psoriasis in Trials 1- 4

	Trial 1		Trial 2		Trial 3		Trial 4	
	Secukinumab 300 mg (N=245) n (%)	Placebo (N=248) n (%)	Secukinumab 300 mg (N=327) n (%)	Placebo (N=326) n (%)	Secukinumab 300 mg (N=59) n (%)	Placebo (N=59) n (%)	Secukinumab 300 mg (N=60) n (%)	Placebo (N=61) n (%)
PASI 90 response	145 (59)	3 (1)	175 (54)	5 (2)	35 (60)	0 (0)	33 (55)	0 (0)
IGA of clear or almost clear	160 (65)	6 (2)	202 (62)	9 (3)	40 (68)	0 (0)	44 (73)	0 (0)

Examination of age, gender, and race subgroups did not identify differences in response to secukinumab among these subgroups.

PASI 90 response at Week 12 was achieved with secukinumab 300 mg and 150 mg compared to placebo in 59% (145/245) and 39% (95/245) versus 1% (3/248) of subjects, respectively (Trial 1) and 54% (175/327) and 42% (137/327) versus 2% (5/326) of subjects, respectively (Trial 2). Similar results were seen in Trials 3 and 4.

With continued treatment over 52 weeks, subjects in Trial 1 who were PASI 75 responders at Week 12 maintained their responses in 81% (161/200) of the subjects treated with secukinumab 300 mg. Trial 1 subjects who were clear or almost clear on the IGA at Week 12 also maintained their responses in 74% (119/160) of subjects treated with secukinumab 300 mg. Similarly in Trial 2, PASI 75 responders maintained their responses in 84% (210/249) of subjects treated with secukinumab 300 mg. Trial 2 subjects who were clear or almost clear on the IGA also maintained their responses in 80% (161/202) of subjects treated with secukinumab 300 mg.

Among the subjects who chose to participate (39%) in assessments of patient reported outcomes, improvements in signs and symptoms related to itching, pain, and scaling, at Week 12 compared to placebo (Trials 1 and 2) were observed using the Psoriasis Symptom Diary©.

3.6.2 Infections

Secukinumab may increase the risk of infections. In clinical trials, a higher rate of infections was observed in secukinumab-treated subjects compared to placebo-treated subjects. In placebo-controlled clinical trials in patients with moderate to severe plaque psoriasis, higher rates of common infections such as nasopharyngitis (11.4% versus 8.6%), upper respiratory tract infection (2.5% versus 0.7%) and mucocutaneous infections with *Candida* (1.2% versus 0.3%) were observed with secukinumab compared with placebo. A similar increase in risk of infection was seen in placebo-controlled trials in patients with psoriatic arthritis and ankylosing spondylitis. The incidence of some types of infections appeared to be dose-dependent in clinical studies. Proper exclusion criteria will be applied in this study to ensure subject safety.

[redacted]

3.6.3 Pre-treatment evaluation for tuberculosis

Evaluate subjects for tuberculosis (TB) infection prior to initiating treatment with secukinumab. Do not administer secukinumab to subjects with active TB infection. Initiate treatment of latent TB prior to administering secukinumab. Consider anti-TB therapy prior to initiation of secukinumab in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving secukinumab should be monitored closely for signs and symptoms of active TB during and after treatment.

3.6.4 Inflammatory bowel disease

Caution should be used when prescribing secukinumab to patients with inflammatory bowel disease. Exacerbations, in some cases serious, occurred in secukinumab-treated patients during clinical trials in plaque psoriasis, psoriatic arthritis and ankylosing spondylitis. In addition, new onset inflammatory bowel disease cases occurred in clinical trials with secukinumab. In an exploratory study in 59 patients with active Crohn's disease, there were trends toward greater disease activity and increased adverse events in the secukinumab group as compared to the placebo group. Patients who are treated with secukinumab should be monitored for signs and symptoms of inflammatory bowel disease.

3.6.5 Hypersensitivity reactions

Anaphylaxis and cases of urticaria occurred in secukinumab-treated subjects in the clinical trials. If an anaphylactic or other serious allergic reaction occurs, administration of secukinumab should be discontinued immediately and appropriate therapy initiated.

3.6.6 Risk of hypersensitivity in latex-sensitive Individuals

The removable cap of the secukinumab prefilled syringe contains natural rubber latex which may cause an allergic reaction in latex-sensitive individuals. The safe use of the secukinumab prefilled syringe in latex-sensitive individuals has not been studied.

3.6.7 Vaccinations

Prior to initiating therapy with secukinumab, consider completion of all age appropriate immunizations according to current immunization guidelines. Subjects treated with secukinumab should not receive live vaccines. Non-live vaccinations received during a course of secukinumab may not elicit an immune response sufficient to prevent disease.

4 Population

The study population will consist of male and female patients (≥18 years of age) with moderate to severe chronic plaque-type psoriasis that requires systemic therapy, which is defined as psoriasis that is inadequately controlled by topical treatments (including topical corticosteroids (TCS)), ultraviolet (UV) light, or systemic therapy.

The goal is to randomize a total of 75 patients in approximately 12 centers in the United States. Since a 30% screen failure rate is expected, approximately 107 patients will be screened.

[redacted]

Patients who discontinue after they have been randomized will not be replaced.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed
2. Males and females ≥18 years of age at the time of screening
3. Clinical diagnosis of chronic plaque-type psoriasis at least 6 months prior to randomization as determined by patient interview of his/her medical history and by confirmation of diagnosis through physical examination by the investigator
4. Moderate to severe plaque psoriasis as defined at baseline by:
   - ≥10% Body Surface Area (BSA) involvement **and**
   - PASI total score of ≥12 **and**
   - IGA mod 2011 score of ≥3 (based on a scale of 0-4)
5. Candidate for systemic therapy, defined as having psoriasis inadequately controlled by:
   - Topical treatment (including topical corticosteroids) **and/or**
   - Phototherapy **and/or**
   - Previous systemic therapy

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Forms of diagnosed psoriasis other than chronic plaque psoriasis (e.g., erythrodermic, generalized or localized pustular psoriasis, or new onset guttate psoriasis)
2. Medication-induced or medication exacerbated psoriasis (e.g., new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium)
3. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17RA receptors (e.g., ixekizumab, or brodalumab)
4. Diagnosis of other active ongoing skin diseases or skin infections (bacterial, fungal, or viral), or inflammatory diseases other than psoriasis that may interfere with the evaluation of psoriasis
5. Ongoing use of treatments prohibited by the protocol (see Section 5.5.8, Table 5-1)
6. Plans for administration of live vaccines during the study period or within 6 weeks before randomization
7. Use of any investigational treatment within 4 weeks prior to Randomization, or within a period of 5 half-lives of the investigational treatment prior to Randomization, whichever is longer

[redacted]

8. Currently enrolled in any other clinical trial involving any investigational agent or device
9. Patients using cholesterol-lowering medication (e.g., statins) who have not been on a stable dose for at least 90 days prior to randomization and who are unable to remain on a stable dose for the duration of the study
10. Pregnant or nursing (lactating) women
11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and for 16 weeks after stopping of study treatment. Basic contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps)
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

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

    NOTE: Women are considered post-menopausal and not of child bearing 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
    - surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. 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 child-bearing potential.
12. Current severe progressive or uncontrolled disease which in the judgment of the investigator renders the patient unsuitable for the trial or puts the patient at increased risk
13. Any underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which, in the opinion of the investigator, significantly immunocompromises the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy
14. Presence of significant medical problems, including but not limited to the following: uncontrolled hypertension with measured systolic >180 mmHg and/or diastolic >95

[redacted]

mmHg; congestive heart failure (New York Heart Association [NYHA] status of class III or IV

15. Fasting blood glucose ≥200 mg/dL and hemoglobin A1c ≥7% at screening; fasting glucose ≥150 mg/dL up to 199 mg/dL will require consultation with the Medical Monitor to confirm eligibility
16. Total white blood cell (WBC) count <2,500/µl, or thrombocytes <100,000/µl, or neutrophils <1,500/µl, or hemoglobin <8.5 g/dL at screening
17. Active systemic infections during 2 weeks prior to randomization (exception: the common cold) or any infection that reoccurs on a regular basis
18. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive or indeterminate QuantiFERON TB-Gold test (QFT) at screening.
    - NOTE: Patients with a positive QFT may participate in the study if a full tuberculosis work up (according to local practice/guidelines) completed within 12 weeks prior to randomization establishes conclusively that the patient has no evidence of active tuberculosis. If the presence of latent tuberculosis is established, then treatment must have been initiated and maintained for at least 4 weeks prior to randomization and the course of prophylaxis is planned to be completed.
19. Positive serology for human immunodeficiency virus (HIV), hepatitis B or C infection at screening
20. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for skin Bowen's disease, squamous cell carcinoma, basal cell carcinoma, actinic keratoses that have been treated, carcinoma *in situ* of the cervix, or non-invasive malignant colon polyps that have been removed)
21. History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to randomization
22. History of hypersensitivity to constituents of the study treatment and/or patients who are allergic to rubber or latex (the needle cap of the single-use prefilled syringe for secukinumab and placebo may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals)
23. Any medical, psychiatric or other condition which, in the investigator's opinion, would preclude the patient from adhering to the protocol or completing the study per protocol
24. Patients who are not able and/or not willing to self-administer secukinumab injections or who have no trained caregiver available to administer these injections

5 Treatment

5.1 Study treatment

All study treatments will be supplied by Novartis and will be labeled appropriately.

All doses of study treatment should be self-administered. Self-administration of the study treatment refers to patient self-injection or injection by a trained caregiver regardless of

[redacted]

whether dosing occurs at the study site or at home. Instruction and training will be provided by site staff to patients/caregivers prior to self-injection.

All doses of study treatment that are administered at the study site should be performed after all study assessments for the visit have been completed.

5.1.1 Study drug – secukinumab

- Secukinumab 150 mg: 1 ml liquid formulation in a single-use prefilled syringe (PFS)

Secukinumab for subcutaneous (s.c.) injection is provided in a PFS containing 150 mg secukinumab. Each secukinumab 300 mg dose is given as two s.c. injections of 150 mg.

5.1.2 Control drug – placebo

- Placebo to secukinumab 150 mg: 1 ml liquid formulation in a single-use prefilled syringe (PFS)

Placebo to secukinumab 150 mg for s.c. injection is provided in a matching PFS. Each PFS contains a mixture of inactive excipients, matching the composition of the secukinumab 150 mg dose. Each placebo dose is given as two s.c. injections of placebo to secukinumab 150 mg.

5.1.3 Additional treatment

No additional treatment beyond the study drug and control drug are included in this trial.

5.2 Treatment groups

At Visit 2/Baseline, eligible patients will be randomized to one of the following two treatment groups in a ratio of 2:1:

Secukinumab group

- Patients (or trained caregivers) will administer a dose of secukinumab 300 mg s.c. (two injections of the 150 mg PFS) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks, starting at Week 8 through Week 48. In order to maintain the blinding for the 12-week, placebo-controlled period, two injections of the placebo PFS will be administered at Weeks 13, 14, and 15 during the Double-blind Induction Period.

Placebo group

- Patients (or trained caregivers) will administer a dose of placebo s.c. (two injections of the placebo PFS) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by a dose after four weeks at Week 8.
- Beginning at Visit 8/Week 12, all patients in the placebo group will be switched to treatment with secukinumab 300 mg s.c. Patients will receive a dose of secukinumab 300 mg s.c. (two injections of the 150 mg PFS) once weekly for five weeks (at Weeks 12, 13, 14, 15, and 16) followed by dosing every four weeks starting at Week 20 through Week 48.

The treatment groups and dosing frequency are also described in Table 5-1 below.

[redacted]

Table 5-1 Overview of study treatment

Treatment group	DB Treatment Period *(Rand – Wk 12 pre-dose)*	DB Induction Period *(Wk 12 – Wk 15)*	OL Treatment Period *(Wk 16 – Wk 52)*
Secukinumab 300 mg			
	2x s.c. secukinumab 150 mg injection at BSL, Wks 1, 2, 3, 4 and 8	2x s.c. secukinumab 150 mg injection at Wk 12 2x s.c. PBO injection at Wks 13, 14 and 15	2x s.c. secukinumab 150 mg injection at four-week intervals from Wks 16 - 48
Placebo (PBO)			
	2x s.c. PBO injection at BSL, Wks 1, 2, 3, 4 and 8	2x s.c. secukinumab 150 mg injection at Wks 12, 13, 14, and 15	2x s.c. secukinumab 150 mg injection at four-week intervals from Wks 16 – 48

DB = Double-blind; OL = Open-label; PBO = placebo; BSL = Baseline; Wk = Week

5.3 Treatment assignment and randomization

At Visit 2/Baseline, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the two treatment groups. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment groups, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to boxes containing the study treatment.

The randomization scheme for patients will be reviewed and approved by a member of the Novartis Biometrics group.

5.3.1 Stratification

Randomization will be stratified by body weight. The stratification ensures balanced allocation of patients to treatment groups within the weight strata. The strata will be "body weight <90 kg" or "body weight ≥90 kg".

Stratification by body weight will occur at Visit 2/Baseline. The body weight collected at Visit 2 will be used for the stratification.

[redacted]

5.4 Treatment blinding

Patients, investigators/site staff, persons performing assessments, and Novartis study personnel will remain blinded to individual treatment assignment from the time of randomization until the final database lock at Week 53, 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 (DSM);
2. The identity of secukinumab and placebo prefilled syringes (PFS) will be concealed by identical packaging, labeling, schedule of administration, and appearance.

At the Week 12 primary analysis time point, there will be a database lock after all patients have completed the Week 12 visit. At that time, only the statistician and programmer(s) from the designated CRO will be unblinded in order to perform the analysis. Results from the analyses of all data through Week 12, including the data for the primary efficacy variable, will be reported. For publication purposes, summary results from the Week 12 primary analysis time point may be shared with the health care community, however individual patient-level data will remain blinded until the end of the trial.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9), at the time of the primary analysis (Week 12) for designated CRO personnel only, and at the conclusion of the study.

A full analysis of all data collected up to Week 53 will be performed when all patients have completed Follow-up Visit 1/Week 53.

5.5 Treating the patient

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

5.5.1 Patient numbering

Each patient is uniquely identified by a Patient Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Patient Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Patient Number from the EDC system to enter data.

If the patient fails to be treated for any reason, the IRT system must be notified that the patient was not treated. The reason for not being treated will be entered on the Screening Study Disposition eCRF.

[redacted]

5.5.2 Dispensing the study drug

Each study site will be supplied by Novartis with secukinumab and placebo treatment in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the two treatment groups. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient.

IRT will assign secukinumab or placebo at each visit from Randomization to Week 48. All boxes of study treatment assigned by the IRT will be recorded/databased in the IRT system.

5.5.3 Handling of study and additional treatment

5.5.3.1 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 designees 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. For any syringe with a technical issue, a description of the issue must be communicated to Novartis Quality Assurance, and the syringe may be required to be returned to Novartis for further assessment. In the event a technical issue with a syringe is identified, site staff should contact their monitor for guidance on the reporting and returns process.

The prefilled syringes (150 mg secukinumab or placebo) sealed in their outer box must be stored in a locked refrigerator between 2° to 8°C (36° to 46°F) and must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations. **Study treatment should <u>not</u> be frozen**. All temperature excursions (either below or above the required, specified temperature range) must be reported to Novartis for review and assessment of impact on the study treatment. In the event of a temperature excursion, site staff should contact their monitor for guidance on the reporting process.

Medication labels will be in English and will comply with US legal requirements. They will include storage conditions for the study treatment but no information about the patient 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. Patients will be asked to return all used/unused study treatment and packaging to the study site.

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

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

All doses of study treatment that are administered at the study site should be performed after all study assessments for the visit have been completed. The first study treatment administration will occur at Visit 2/Baseline after inclusion/exclusion criteria has been confirmed and all scheduled assessments have been performed.

The prefilled syringes will be provided by the site staff to the patient, who will then self-inject the study treatment. Site staff should remove the assigned study treatment from the refrigerator and allow the syringes to reach room temperature in their unopened box (approximately 15-30 minutes) before self-injection by the patient.

Detailed instructions on the self-administration of the study treatment will be described in the Instructions For Use (IFU), a copy of which will be provided to each patient. At the Baseline visit, the patient will be instructed by the site staff (using the IFU) on how to self-inject with the PFS. Patients will be asked to raise any questions if they have any.

Starting at Visit 3/Week 1, patients will be asked to refer to the IFU and to proceed with self-injection of the study treatment at the study site under the supervision of site staff.

Patients must inject the study treatment into the appropriate body site (thighs, abdomen, upper outer arm). Study treatment should not be injected into areas where the skin is tender, bruised, red, scaly or hard, or in an area of skin affected by psoriasis. Areas with scars or stretch marks should be avoided. As possible throughout the trial, the injection site should be rotated from visit to visit.

All self-injections during the Double-blind Treatment Period will take place at the study site; during the Double-blind Induction and Open-label Treatment Periods, self-injections will occur both at the study site and at home (refer to Table 6-1).

Used study treatment syringes should be disposed immediately after use in a sharps container.

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the *study treatment as prescribed.*

Study treatment administration at home

If the patient or caregiver is not able/confident to perform home administration, the patient will be allowed to return to the site for administration of the medication. During those visits, no additional assessments will be required.

Patients will be instructed to contact the investigator/site staff prior to self-administration at home if they are experiencing any AE/SAEs or have any concerns. Additionally, site staff will contact patients via telephone at the time of scheduled at-home dosing to check compliance and to ensure completion of the dosing log.

[redacted]

Patients will be provided with the following items to facilitate the at-home injections of study treatment: an insulated bag with cool gel packs to transport the study treatment from the site to the patient's home; alcohol swabs and gauze pads; a sharps container for immediate disposal of the used syringes; a copy of the IFU; and a paper Self-administration Log to record the dates and times of the at-home doses.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted.

Study treatment interruption is permitted if, in the opinion of the investigator, a subject is deemed to be placed at a 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 started again at the next scheduled visit after resolution of the safety risk.

5.5.6 Rescue medication

Use of rescue medication is not permitted during the study.

5.5.7 Concomitant treatment

The investigator must instruct the patient to notify study staff about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the Prior and Concomitant Medications eCRF or the Surgical and Medical Procedures eCRF as appropriate.

Each concomitant drug or therapy/procedure must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the study Medical Monitor before randomizing a patient or allowing a new medication or therapy/procedure to be started.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-2 is NOT allowed for any indication after the start of study treatment; the use of these treatments could confound the efficacy of the study drug. Wash-out periods for these treatments are provided in Table 5-2. If the use of any of these treatments is required, then the patient must NOT be randomized into the study.

The investigator/qualified site staff must instruct the patient to notify them about any new treatments he/she initiates during the study. All prohibited medications and significant non-drug therapies administered after the patient starts study treatment must be listed on the eCRF.

If a prohibited treatment listed in Table 5-2 is used after the start of study treatment, the patient must discontinue use of the prohibited treatment if he/she wishes to continue in the study.

If, in the investigator's clinical judgment, the patient's use of a prohibited treatment presents an undue safety risk for the patient, the patient **must** discontinue study treatment; if a

[redacted]

patient receives a live virus vaccination during the study, the patient **must** discontinue study treatment (see Section 5.6.2).

Table 5-2 Prohibited treatment

Prior Therapy (Before Visit 2/Baseline)	
Prohibited Treatments[1,2]	**Washout Period (before Randomization)**
Secukinumab	No prior use allowed
Any biologic drug directly targeting IL-17 or the IL-17 receptor (e.g., ixekizumab or brodalumab)	No prior use allowed
Alefacept, briakinumab, efalizumab, ustekinumab	24 weeks
Biological immunomodulating agents other than above (e.g., adalimumab, infliximab, etanercept)	12 weeks
Other systemic immunomodulating treatments[3] [e.g., MTX, cyclosporine A, corticosteroids (oral, i.v., transdermal)[3], cyclophosphamide]	4 weeks
Other systemic psoriasis treatments (e.g., retinoid, fumarates)	4 weeks
Photo chemotherapy (e.g., PUVA)	4 weeks
Phototherapy (e.g., UVA, UVB)	2 weeks
Medicated psoriasis shampoo (including OTC)	2 weeks
Topical treatment that is likely to impact signs and symptoms of psoriasis (e.g., vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids)	2 weeks
Topical Corticosteroids (TCS) any potency on areas of psoriasis	2 weeks
Live virus vaccines	6 weeks
An investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Any other treatment known to worsen psoriasis (e.g., beta-blockers, calcium channel blockers)	Stable dose for at least 4 weeks prior to randomization
Cholesterol-lowering medication (e.g., statins)	Stable dose for ≥90 days prior to randomization and remain stable for duration of the study

Concomitant Therapy with TCS (after Visit 2/Baseline)	
Topical Corticosteroids (TCS)	**Concomitant Use**
TCS on areas of psoriasis (including scalp)	Hydrocortisone 2.5% cream is allowed on face and intertriginous areas; medicated OTC shampoos are allowed for the scalp
TCS mild to moderate potency used for up to 7 consecutive days per event for an indication other than psoriasis and on areas **not** affected by psoriasis	Allowed during the study

[redacted]

[1] If the prohibited treatment was used during the study for any indication, the patient must discontinue use of the prohibited treatment if he/she wishes to continue in the study.

[2] In case of undue safety risk for the patient as determined by the investigator, the patient should discontinue study treatment. If the patient receives a live virus vaccination during the study, the patient must discontinue study treatment.

[3] Inhaled CS with only a topical effect (e.g., to treat asthma) are not considered "**systemic** immunomodulating treatments" and are therefore acceptable as concomitant medication.

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient 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 patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient 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)
- patient number

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

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

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

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when (s)he has completed the last visit planned in the protocol.

Continuing care should be provided by the investigator and/or referring physician based on patient availability for follow-up.

5.6.2 Discontinuation of study treatment

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

[redacted]

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

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient decision
- Pregnancy (see Section 6.7.5 and Section 7.4)
- AEs that in the judgment of the investigator/qualified site staff, taking into account the patient's overall status prevent the patient from continuing study treatment
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study
- Ongoing use of prohibited treatment, use of a prohibited treatment that results in an undue safety risk for the patient as per the investigator's clinical judgment, or receipt of a live virus vaccine during the study (as detailed in Section 5.5.8)
- Any situation in which study participation might result in a safety risk to the patient
- Emergency unblinding

The investigator/site staff must contact the IRT to register the patient's discontinuation from study treatment.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

5.6.2.1 End of treatment visit

Patients who discontinue study treatment should return to the study site for an end of treatment visit. The end of treatment visit should be scheduled to occur approximately four (4) weeks after the patient's last dose of study treatment. Discontinuation during:

- **Double-blind Treatment Period:** For patients who discontinue study treatment prematurely before the end of the Double-blind Treatment Period, the Visit 8/Week 12 (EOT1) assessments should be performed. [redacted]
- **Double-blind Induction or Open-label Treatment Periods:** For patients who discontinue study treatment prematurely before the end of the Double-blind Induction or Open-label Treatment Periods, the Visit 15/Week 52 (EOT2) visit should be performed. [redacted]

Assessments scheduled to be performed during the appropriate end of treatment visit per Table 6-1 should be completed and recorded in the eCRF. The investigator must determine

[redacted]

the primary reason for the patient's premature study discontinuation and record this information on the eCRF.

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material.

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient'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 patient 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 patient's study withdrawal should be made as detailed in Table 6-1.

5.6.4 Loss to follow-up

For patients 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 patient, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrollment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. 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 patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

[redacted]

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "X" when the assessments are performed. An "S" indicates the data for that assessment reside in the source documents at the site.

Patients must be seen for all visits on the designated day per the original planned visit schedule or as close as possible to it. Every effort should be made to respect the time frame for all visits, particularly the Week 12 and Week 52 visits.

6.1 Rescreening

Rescreening may be allowed under certain conditions. Requests from the investigator/site staff to rescreen patients will be handled on a case-by-case basis with Medical Monitor approval required before proceeding with the rescreening. Rescreening cannot be done if a patient was previously randomized into the study.

If a patient rescreens for the study, the patient must sign a new ICF and be issued a new patient number prior to any screening assessments being conducted under the new patient number. The date of the new informed consent signature must be entered on the Informed consent eCRF to correspond to the new patient number.

For rescreening, all screening assessments must be performed per protocol, except for the tuberculosis (TB) work up (if applicable). If the date of the TB work up is less than 12 weeks from the projected randomization date, then it is not required that the TB work up be repeated; however, the rescreened patient MUST repeat the QuantiFERON test performed by the central laboratory.

6.2 Unscheduled visits

Patients may be seen at any time for an unscheduled visit, e.g., if they experience deterioration of psoriasis or suspected AEs. The assessments performed at an unscheduled visit are at the discretion of the investigator/qualified site staff. During an unscheduled visit, study treatment will not be administered.

[redacted]

Table 6-1 Assessment schedule

Period	SCR	Double-blind Treatment Period							Double-blind Induction Period			Open-label Treatment Period										F-up	Unscheduled Visit[2]	Notes
Visit	1	2	3	4	5	6	7	8/ EOT1	9			10		11		12		13		14	15/ EOT2	F1[1]		
Week	-4 to BL	BL	1	2	3	4	8	12	13	14	15	16	20	24	28	32	36	40	44	48	52	53		
Assessment Day	≤-28 to BL	1	8	15	22	29	57	85	92	99	106	113	141	169	197	225	253	281	309	337	365	372		
Obtain informed consent	X																							
Demographics	X																							See Section 6.4.1
Inclusion/exclusion criteria	X	X																						See Section 4.1 and Section 4.2
Smoking and alcohol history	X																							See Section 6.4.3 and Section 6.4.4
Psoriasis medical history/ prior psoriasis therapies	X																							See Section 6.4.2
Cardiovascular medical history	X																							See Section 6.4.5
Other medical history/ current medical conditions	X																							See Section 6.4.6
Prior/concomitant medications / Surgical and medical procedures	Update as necessary																							See Section 6.4.7
(s)AE assessment	Update as necessary																							See Section 7
Physical examination	S	S						S						S							S		S	See Section 6.7.1
Height	X																							See Section 6.7.3
Weight	X	X				X	X	X				X		X		X		X		X	X		X	See Section 6.7.3
Waist circumference		X						X						X							X			See Section 6.7.3

[redacted]

Period	SCR	Double-blind Treatment Period							Double-blind Induction Period			Open-label Treatment Period										F-up	Unscheduled Visit[2]	Notes
Visit	1	2	3	4	5	6	7	8/ EOT1	9			10		11		12		13		14	15/ EOT2	F1[1]		
Week	-4 to BL	BL	1	2	3	4	8	12	13	14	15	16	20	24	28	32	36	40	44	48	52	53		
Assessment Day	≤-28 to BL	1	8	15	22	29	57	85	92	99	106	113	141	169	197	225	253	281	309	337	365	372		
BMI calculation		X						X						X							X			See Section 6.7.3; calculated in eCRF
Vital signs	X	X				X	X	X				X		X		X		X		X	X		X	See Section 6.7.2
Lab analysis: Hematology[3]	X							X						X							X		X	See Section 6.7.4.1
Lab analysis: Clinical chemistry[3]	X							X						X							X		X	See Section 6.7.4.2
hs-CRP[3]		X						X						X							X		X	See Section 6.7.4.3
HbA1c[3]	X	X						X						X							X		X	See Section 6.7.4.4
Fasting labs: plasma glucose, insulin, lipids[3]	X	X						X						X							X		X	See Section 6.7.4.5
HOMA-IR calculation		X						X						X							X			See Section 6.7.4.5; calculated and reported by central lab
Serology lab analysis: HIV, Hep B and Hep C[3]	X																						X	See Section 6.7.4.6
QuantiFERON® TB-Gold In-Tube test[3]	X																						X	See Section 6.4.8
Serum pregnancy test[3]	X																						X	See Section 6.7.5
Urine pregnancy test (local)		X						X													X		X	See Section 6.7.5

[redacted]

Period	SCR	Double-blind Treatment Period							Double-blind Induction Period			Open-label Treatment Period										F-up	Unscheduled Visit[2]	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ EOT1**	**9**			**10**		**11**		**12**		**13**		**14**	**15/ EOT2**	**F1[1]**		
Week	**-4 to BL**	**BL**	**1**	**2**	**3**	**4**	**8**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**53**		
Assessment Day	**≤-28 to BL**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**372**		
[redacted]																								
PASI	X	X				X	X	X				X		X		X		X		X	X		X	See Section 6.6.5
Alcohol and tobacco use assessments								X						X							X			See Section 6.4.3 and Section 6.4.4
Randomization via IRT		S																						See Section 5.3
Patient self-administration of study treatment at site		X	X	X	X	X	X	X	X			X		X		X		X		X				See Section 5.5.4
Dispense study treatment to patient for at-home dosing									S			S		S		S		S						See Section 5.5.4
[redacted]																								

Period	SCR	Double-blind Treatment Period							Double-blind Induction Period			Open-label Treatment Period										F-up	Unscheduled Visit[2]	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ EOT1**	**9**			**10**		**11**		**12**		**13**		**14**	**15/ EOT2**	**F1[1]**		
Week	**-4 to BL**	**BL**	**1**	**2**	**3**	**4**	**8**	**12**	**13**	**14**	**15**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**53**		
Assessment Day	**≤-28 to BL**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**372**		
Patient self-administration of study treatment at home and completion of Self-Administration Log										X	X		X		X		X		X					See Section 5.5.4 and Section 6.5
At-home Dosing Phone Reminder										S	S		S		S		S		S					See Section 6.5
Check Self-Administration Log and returned used/unused study treatment and packaging												S		S		S		S		S				See Section 6.5

(S)AE = (serious) adverse event; BL = Baseline; BMI = body mass index; FACS = fluorescence activated cell sorting; F-up = Follow-up Period; hs-CRP = high sensitivity C-reactive protein; HIV = human immunodeficiency virus; HOMA-IR = homeostatic model assessment of insulin resistance; IRT = interactive response technology; [redacted]; SCR = Screening; TB = tuberculosis;

Weeks in dark/grey columns: At these weeks, patients are expected to self-administer the study treatment at home. If the patient or caregiver cannot administer the drug at home, then the patient may return to the site for study treatment administration.

X = assessment to be recorded on clinical data base; S = assessment to be recorded in source documentation only

1. Patients who undergo skin biopsies at Visit 15/Week 52 will return to the site for completion of Visit F1; additionally, all patients who discontinue prematurely from the study **and** who undergo skin biopsies at their end of treatment visit (either Visit 8/EOT1 or Visit 15/EOT2) will return to the site for completion of Visit F1
2. Unscheduled Visit: assessment(s) performed at an unscheduled visit are at the investigator's discretion
3. Samples will be analyzed by a central laboratory

[redacted]

[redacted]

Table 6-2 Assessment schedule for healthy control cohort

Visit	1/EOT[1]	F2	Notes
Obtain informed consent	X		
Demographics	X		See Section 6.4.1
Inclusion/exclusion criteria	S		See Section 3.1.6
Smoking and alcohol history	X		See Section 6.4.3 and Section 6.4.4
Cardiovascular medical history	X		See Section 6.4.5
Other medical history/ current medical conditions	X		See Section 6.4.6
Prior/concomitant medications / Surgical and medical procedures	X		See Section 6.4.7
(s)AE assessment	X	X	See Section 7
Height	X		See Section 6.7.3
Weight	X		See Section 6.7.3
Waist circumference	X		See Section 6.7.3
BMI calculation	X		See Section 6.7.3; calculated in eCRF
Vital signs	X		See Section 6.7.2
Lab analysis: Hematology[2]	X		See Section 6.7.4.1
Lab analysis: Clinical chemistry[2]	X		See Section 6.7.4.2
hs-CRP[2]	X		See Section 6.7.4.3
HbA1c[2]	X		See Section 6.7.4.4
Fasting labs: plasma glucose, insulin, lipids[2]	X		See Section 6.7.4.5
HOMA-IR calculation	X		See Section 6.7.4.5; calculated and reported by central lab
Urine pregnancy test (local)	X		See Section 6.7.5
[redacted]			

(S)AE = (serious) adverse event; BMI = body mass index; FACS = fluorescence activated cell sorting; F2 = Follow-up Visit 2; hs-CRP = high sensitivity C-reactive protein; HOMA-IR = homeostatic model assessment of insulin resistance; [redacted]

X = assessment to be recorded on clinical data base; S = assessment to be recorded in source documentation only

1. Visit 1 assessments may or may not occur on the same day, however all assessments should be performed and completed within 7 calendar days of the informed consent date
2. Samples will be analyzed by a central laboratory

[redacted]

[redacted]

6.3 Information to be collected on screening failures

All patients who sign the informed consent but discontinue prior to randomization at Visit 2/Baseline are considered to be screen failures.

If a patient discontinues prior to randomization, the IRT provider must be notified, and the reason for the patient not being randomized will be entered on the Screening Phase Disposition eCRF. The Screening Visit Date, the Demography eCRF, the Informed Consent eCRF, the Inclusion/Exclusion eCRF, and the Subject Re-screening eCRF must be completed.

The Adverse Event eCRF should be completed for any SAEs that occurred during the screening period. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. The Withdrawal of Consent eCRF must be completed if consent was withdrawn during the screening period before the patient was randomized.

6.4 Patient demographics/other baseline characteristics

All baseline assessments will be performed prior to the first study treatment administration.

6.4.1 Demographics

Patient demographic data will be collected at Visit 1/Screening. Data to be collected on all patients include: date of birth, patient initials, age, sex, race, ethnicity, and child-bearing potential (for females only).

6.4.2 Psoriasis history / Prior psoriasis therapies

Disease history will be collected at Visit 1/Screening. The information to be collected and entered in the Psoriasis History eCRF and Prior Psoriasis Therapy eCRF includes the following:

- start date of plaque psoriasis;
- previous psoriasis treatments (including previous use of biologic therapies, as well as phototherapy and/or photo chemotherapy), duration of exposure, and the reason for discontinuation of each therapy;
- presence of psoriatic arthritis and the date of first diagnosis (by a physician).

6.4.3 Smoking history

The current and/or previous use of tobacco products will be recorded, as well as the estimated number of pack-years based on the approximate consumption per year. Non-smokers will be advised to not start smoking during the study.

Current tobacco use will be assessed throughout the duration of the study as the scheduled visits as indicated in Table 6-1.

6.4.4 Alcohol use history

The current and/or previous use of alcohol will be recorded. This includes the estimated number of alcoholic drinks consumed on average per day, and the date alcohol was last consumed.

Current alcohol use will be assessed throughout the duration of the study at the scheduled visits as indicated in Table 6-1.

6.4.5 Comorbidities – cardiovascular history

Information pertaining to cardiovascular medical history assessed prior to randomization should be reported on the Cardiovascular History eCRF.

6.4.6 Relevant medical history/current medical conditions

Relevant medical history and current medical conditions prior to providing informed consent (not including psoriasis or psoriatic arthritis) will be recorded in the Medical History eCRF. Whenever possible, diagnoses and not symptoms will be recorded.

Significant findings that are observed after the patient has signed the informed consent form and that meet the definition of an AE must be recorded in the AE eCRF. Investigators will have the discretion to record abnormal test findings on the Medical History eCRF when in their judgment, the test abnormality occurred prior to the informed consent signature.

6.4.7 Prior and concomitant medications

Concomitant medications and prior medications taken over the six (6) months preceding study enrollment will be captured in the Prior and Concomitant Medication eCRF at the screening visit, and updated at Visit 2/Baseline.

6.4.8 Determination of tuberculosis status

Determination of tuberculosis (TB) status will be required before administration of study treatment. TB status must be determined by medical history, signs, symptoms, and TB testing (QuantiFERON-TB Gold assay). Any significant findings will be recorded in the appropriate eCRF(s), as necessary.

If the QuantiFERON-TB Gold Assay test is positive or indeterminate, a TB workup should be performed as defined by local guidelines to determine the patient's TB status.

6.4.8.1 QuantiFERON TB-Gold In-Tube assay

A QuantiFERON® TB-Gold In-Tube assay will be performed to assess the TB status at screening for all patients. This test will only be used to determine patient's eligibility for the trial. The test will be used to screen the patient population for latent tuberculosis infection (Doherty, Van Vorhees and Lebwohl 2008).

This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin vaccination or exposure to other Mycobacteria species.

This test, in contrast to the purified protein derivative (PPD) skin test, is also insensitive to a booster effect since the patient is not exposed to the vaccine. The assay measures the production of interferon-gamma and presents it relative to a negative and a positive control sample (Manuel and Kumar 2008).

[redacted]

The QuantiFERON®-TB Gold assay test will be supplied by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the Laboratory Manual.

The results of a TB workup for a patient with a positive or indeterminate test must be recorded in the eCRF.

- If the test result is **negative**, the patient may be randomized
- If the test result is **positive**, the investigator should perform a TB workup for the test result as per local procedures.
  - Patients **positive** for latent TB per workup may be randomized to the study if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration.
  - Patients **positive** for active TB per workup are not eligible for the study.
  - Patients **negative** for TB per workup (no signs of latent or active TB) may be randomized to the study.
- If the test result is **indeterminate**, it is **recommended to repeat the test once**. The investigator may decide to skip the repetition of the test and proceed directly to the workup (however this is not recommended). If a TB workup was conducted prior to screening, results from the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to randomization.
  - If the second test is negative, the patient may be randomized.
  - If the second test is positive or indeterminate, the investigator should perform a TB workup as per local guidelines. The patient will not be eligible for randomization if: "active tuberculosis is present", or if "latent tuberculosis is present" and is untreated as per local guidelines.

Refer to Section 14 Appendix 2 to see a schematic of the tuberculosis screening process and patient eligibility with respect to TB testing.

6.4.9 Other baseline characteristics

Baseline characteristic data to be collected on all patients include (see also Table 6-1):

- vital signs, hematology, clinical chemistry, viral serology (HIV, Hepatitis B and Hepatitis C), serum pregnancy, height, weight; BMI, HOMA-IR, hs-CRP, HbA1c, PASI, [redacted].

6.5 Treatment exposure and compliance

All administered doses of secukinumab or placebo will be recorded on the Dosage Administration Record eCRF. Compliance will be assessed at each visit by Novartis and CRO study personnel using the Dosage Administration Record eCRF, medication numbers, Drug Label Form information, empty medication boxes/outer packaging brought back to site by patient, and information collected by IRT.

Patients will be provided with a Self-Administration Log at Visit 8/Week 12 to record the date and time of all at-home study treatment administrations during the Double-blind Induction and Open-label Treatment Periods. Patients will be instructed to return to the study site at

[redacted]

each scheduled visit with their completed Self-Administration Log, where the dosing information will be transcribed by site staff into the Dosage Administration Record eCRF. Patients will also be instructed to return all used/unused study treatment and packaging to the study site at each visit as part of the compliance check. The patient's Self-Administration Log will be retained in the patient's source documents.

The investigator/qualified site staff should promote compliance by instructing patients to attend the study visits as scheduled, to take the study treatments exactly as prescribed, and by reiterating that compliance is necessary for patient safety and the validity of the study.

Additionally, site staff will contact patients via telephone at the time of scheduled at-home dosing to check compliance and to ensure completion of the Self-Administration Log. Likewise, patients should be instructed to contact the investigator/qualified site staff if he/she is unable for any reason to attend a study visit as scheduled, or if he/she is unable for any reason to take the study treatment at home as prescribed.

6.6 Efficacy

Primary efficacy variables are response of psoriasis skin lesions to treatment as measured by:

- Response in skin histology/K16 expression to treatment (yes, no)
- PASI 90 (yes, no).

The primary analysis time point will be at Week 12.

Results for the data collected from the assessments in Section 6.6.2 and Section 6.6.3 below will be included as a separate appendix to the Clinical Study Report (CSR).

[redacted]

[redacted]

[redacted]

6.6.5 Assessment of total Body Surface Area (BSA) and Psoriasis Area and Severity Index (PASI)

The investigator or trained qualified designee will complete the PASI assessment at scheduled visits as indicated in Table 6-1. Whenever possible, the same evaluator should perform this assessment at all study visits for a given patient.

The total BSA affected by plaque psoriasis will be estimated by the investigator/trained qualified designee from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for full details of the PASI assessment). The following calculations will be done electronically: each reported percentage will be multiplied by its respective body region corresponding factor (head=0.1, trunk=0.3, upper limbs=0.2, lower limbs=0.4). The resulting four percentages will be added up to estimate the total BSA affected by plaque psoriasis.

A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) will be derived as indicated in Table 6-4. The head, trunk, upper limbs and lower limbs are assessed separately by the investigator/trained qualified designee for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. The following practical details help the assessment:

1. The neck is assessed as part of the head
2. The axillae and groin are assessed as part of the trunk
3. The buttocks are assessed as part of the lower limbs
4. When scoring the severity of erythema, scales should not be removed.

Because the head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the body surface area, respectively, the PASI score is calculated electronically within the eCRF using the following formula:

$$PASI = 0.1(E_H+I_H+D_H)A_H + 0.2(E_U+I_U+D_U)A_U + 0.3(E_T+I_T+D_T)A_T + 0.4(E_L+I_L+D_L)A_L$$

The keys for the letters are provided in Table 6-4.

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0.

The baseline value for analysis of the PASI is collected at Visit 2/Baseline. A copy of the PASI worksheet is provided in Section 16 Appendix 4.

Table 6-4 PASI scoring system

Body region	Erythema (E)	Thickening - plaque elevation, induration (I)	Scaling – desquamation (D)	Area score – based on true area % (A)*
Head (H)†	0=none	0=none	0=none	0=no involvement
	1=slight	1=slight	1=slight	1=>0-<10%
	2=moderate	2=moderate	2=moderate	2=10-<30%
	3=severe	3=severe	3=severe	3=30-<50%

[redacted]

Body region	Erythema (E)	Thickening - plaque elevation, induration (I)	Scaling – desquamation (D)	Area score – based on true area % (A)*
	4=very severe	4=very severe	4=very severe	4=50-<70% 5=70-<90% 6=90-100%
Trunk (T)‡	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 6=90-100%
Upper limbs (U)	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 6=90-100%
Lower limbs (L)§	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 6=90-100%

*Percentage (not score) of body region (not whole body) affected will be entered in the eCRF

†Neck is assessed as part of the Head (H) body region

‡Axillae and groin are assessed as part of the Trunk (T) body region

§Buttocks are assessed as part of the Lower limbs (L) body region

Definitions of efficacy variables based on PASI

The following definitions will be used in this study based on the CHMP guidelines for psoriasis (CHMP/EWP/2454/02 2004):

- [redacted]
- **PASI 90 response**: patients achieving ≥90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders
- [redacted]

[redacted]

6.6.6 Appropriateness of efficacy assessments

Determining the response of skin to psoriasis treatment, by using combined genetic studies including microarray technology with histopathology over the course of anti-TNF alpha treatment (etanercept*)* and anti-IL-17A (ixekizumab) treatment has been used previously and are well established methodology (Zaba et al 2007; Zaba et al 2009; Wang et al 2014).

[redacted]

Flow cytometry has been used to measure T-cell activation for skin diseases such as atopic dermatitis and psoriasis (Czarnowicki et al 2015).

The PASI is a standard and validated measurement for chronic plaque psoriasis.

[redacted]

6.7 Safety

All blood draws and safety assessments must be performed prior to study treatment administration. Appropriate safety assessments (e.g., evaluation of AEs and SAEs including injection site reactions) should be repeated after dosing with study treatment.

6.7.1 Physical examination

The physical examination, including general appearance, will be performed at the scheduled study visits as indicated in Table 6-1.

The physical examination is performed by a professionally trained physician or health professional licensed to perform physical examinations, and listed on FDA Form 1572.

If indicated, based on medical history and/or symptoms, additional exams will be performed at the discretion of the investigator.

If possible, assessments for an individual patient should be performed by the same member of the study site staff throughout the study.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the patient signing informed consent must be included in the Medical History eCRF. Significant findings made after the signing of the informed consent which meet the definition of an AE (see Section 7) must be recorded on the AE eCRF.

[redacted]

6.7.2 Vital signs

Vital signs will be performed at the scheduled study visits as indicated in Table 6-1. Vital signs include blood pressure (BP) and pulse measurements. BP will be measured using a standard sphygmomanometer with an appropriate sized cuff.

All clothing that covers the location of the cuff placement is to be removed by the patient. The patient should be asked to sit comfortably with the back supported and legs uncrossed; the arm should be supported so that the middle of the cuff is level with the right atrium (mid-point of the sternum). The patient should be instructed not to talk and relax as much as possible while the measurement is being taken. The measurement should be taken after the patient has been in a seated position and has been resting for 5 minutes (Pickering et al 2005). Every effort should be made to use the same arm for the patient for all vital signs assessments and where possible, the same person performing the assessment.

Normal blood pressure will be defined as a systolic pressure of 90 to <120 mmHg, and a diastolic blood pressure of 60 to <80 mmHg under the measurement conditions outlined above. Notable blood pressure will be hypertension (systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg) or hypotension (systolic blood pressure of <90 mmHg and/or a diastolic blood pressure of <60 mmHg). A blood pressure indicative of prehypertension (systolic blood pressure of 120 to <140 mmHg and/or diastolic blood pressure of 80 to <90 mmHg) will not be regarded as notable (Chobanian et al 2003).

A normal pulse rate will be defined as a rate of 60 to 100 beats per minute (bpm) under the measurement conditions outlined above. Notable pulse rates are a rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia).

Whether action needs to be taken to address notable vital signs values will be decided by the investigator, taking into account the overall status of the patient. No specific action is pre-defined as part of the study protocol.

6.7.3 Height and weight and waist circumference

The measurements will be performed at scheduled visits as indicated in Table 6-1.

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. The body weight recorded at Visit 2/Baseline will be used to stratify randomization at Visit 2.

Waist circumference to the nearest centimeter (cm) will be measured using a tape measure. Starting at the top of the hip bone, bring the tape measure all the way around so that it is level with the belly button. Make sure the tape measure is not too tight and that it is straight. The patient should be instructed not to hold their breath during the measurement.

Body Mass Index (BMI) will be calculated within the eCRF.

6.7.4 Laboratory evaluations

Laboratory evaluations will be performed at the scheduled study visits as indicated in Table 6-1.

[redacted]

A central laboratory will be used for analysis of all specimens 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 ranges, and notable values.

Whether or not any action needs to be taken to address notable laboratory values will be determined by the investigator/qualified site staff, taking into account the overall status of the patient. No specific action is pre-defined within this study protocol.

6.7.4.1 Hematology

Hematology assessments will be performed at the scheduled visits as indicated in Table 6-1 and include: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count.

6.7.4.2 Clinical chemistry

Serum chemistry panel will be performed at the scheduled visits as indicated in Table 6-1 and includes: urea, creatinine, total bilirubin, alanine transaminase (ALT)/serum glutamic pyruvate transaminase (SGPT), aspartate transaminase (AST)/serum glutamic oxaloacetic transaminase (SGOT), gamma glutamyl transpeptidatse (GGT), and alkaline phosphatase.

6.7.4.3 High-sensitivity C-reactive protein

High-sensitivity C-reactive protein (hs-CRP) will be measured by the central laboratory at the scheduled visits as indicated in Table 6-1.

6.7.4.4 Hemoglobin A1c

Hemoglobin A1c (HbA1c) will be measured by the central laboratory at the scheduled visits as indicated in Table 6-1.

6.7.4.5 Fasting laboratory evaluations and HOMA-IR

Fasting (minimum 8 hour duration with water *ad libitum*) laboratory tests will be performed at scheduled visits as indicated in Table 6-1 and will include:

- plasma glucose
- insulin
- lipids

Homeostatic model assessment of insulin resistance (HOMA-IR) values will be reported by the central laboratory at the scheduled visits as indicated in Table 6-1.

6.7.4.6 Viral serology

Viral serology will be performed at screening and will include:

[redacted]

- Hepatitis screening: Hepatitis B surface antigen (HBsAg); Hepatitis C virus antibody (HCVAb)
- HIV screening: HIV 1/2

6.7.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum β-hCG test performed at screening (Visit 1).

All women of childbearing potential will also have a urine pregnancy test performed locally at Visit 2/Baseline. Visit 8/Week 12, and Visit 15/Week 52.

Any woman with a confirmed positive pregnancy test during screening is not eligible for randomization.

A positive urine pregnancy test during the study requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, the patient must be discontinued from the study as described in Section 5.6.2.

6.7.6 Appropriateness of safety measurements

The safety assessments selected for this study are reliable and standard measures for a biologic immunomodulating agent in adult patients with psoriasis.

6.8 Other assessments

No additional tests will be performed on patients entered into this study.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient *after providing written informed consent* for participation in the study until the end of study visit. 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 occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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,

[redacted]

- 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 a patient with underlying disease. Investigators have the responsibility for managing the safety of individual patients and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Section 13 Appendix 1.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- 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
- its relationship to the study treatment
  - Yes
  - No
- its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
- whether it constitutes a serious adverse event (SAE - see Section 7.2 for definition of SAE) and which seriousness criteria have been met
- action taken regarding study treatment

  All adverse events must be treated appropriately. Treatment may include one or more of the following:
  - no action taken (e.g. further observation only)
  - study treatment dosage increased/reduced
  - study treatment interrupted/withdrawn
- concomitant medication
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

Worsening of psoriasis in this study is evaluated via the use of the PASI [redacted] and is not expected to be captured as an AE in the eCRF. Exceptions include cases where: a) a new type of psoriasis is diagnosed, e.g. guttate psoriasis, or b) the worsening of psoriasis is so severe that a qualitatively different status is reached.

[redacted]

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product 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 has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

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:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - 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
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient 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 Annex IV, ICH-E2D Guideline).

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

[redacted]

patient or might require intervention to prevent one of the other outcomes listed above. 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 Annex IV, ICH-E2D Guideline).

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

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis safety if the investigator suspects a causal relationship to 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.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to study treatment, complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

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 Drug Safety and Epidemiology 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.

7.3 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, patient or consumer (EMA definition).

[redacted]

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 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.

Table 7-1 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

7.4 Pregnancy reporting

To ensure patient 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 must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on an SAE form.

8 Data review and database management

8.1 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 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 patient 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 and identify risks and 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 patient 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 patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

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 patients will be disclosed.

8.2 Data collection

The trial (including the control cohort of healthy volunteers) will be conducted in a fully validated Data Capture system which conforms to US CRF 21 Part 11 requirements. Investigator site staff will not be given access to the system until they have been trained. Designated investigator staff will enter the data required by the protocol into the Data Capture system. Automatic validation programs within the system check for data discrepancies in the CRFs and by generating appropriate error messages, allow the data to be confirmed or corrected by the investigator staff. The investigator staff must certify that the data entered are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff [or CRO working on behalf of Novartis] review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an

electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies 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).

Randomization codes and data about all study drug(s) dispensed to the patient 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 IRT database. The database will be sent electronically to Novartis (or a designated CRO).

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.

The occurrence of relevant protocol deviations will be determined. After these 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.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

A designated Contract Research Organization will perform the statistical analysis.

It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of patients will be available for analysis.

The analysis will be conducted on all patient data at the end of Week 12 and at the time the trial ends at Week 53. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Efficacy, safety, and other data will be summarized for all weeks up to Week 53. For continuous variables, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum) at each time point and for change

from baseline to each time point will be reported by treatment group. For discrete variables, frequency counts and percentages at each time point will be reported by treatment group.

Primary [redacted] efficacy variables will be summarized for lesional [redacted] samples.

9.1 Analysis sets

The following analysis sets will be used for the statistical reporting and analyses:

Randomized Set: The Randomized Set includes all randomized patients.

Safety Set: The Safety Set includes all patients who received at least one dose of study medication. Patients will be included in the analysis according to treatment received.

Full Analysis Set: The Full Analysis Set comprises all patients to whom study medication has been assigned. Patients inappropriately randomized (e.g., IRT was called in error for randomization of a screen failed patient) will be excluded from this analysis set. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

9.2 Patient demographics and other baseline characteristics

Data will be summarized by stratum with respect to demographic and baseline characteristics of all patients for the Randomized Set and the Full Analysis Set.

9.3 Treatments

The number of patients and the length of time (in days) exposed to each treatment will be summarized for the Safety Set.

Concomitant medications will be summarized by treatment using frequency counts and percentages for the Safety Set.

Any condition entered as medical history or current medical condition at baseline will be coded using the MedDRA dictionary for the Safety Set. They will be summarized by system organ class and preferred term of the MedDRA dictionary.

9.4 Analysis of the primary variable(s)

9.4.1 Variable(s)

Response of psoriasis skin lesions to treatment as measured by:

a. Response in skin histology/K16 expression to treatment (yes, no)
b. PASI 90 (yes, no)

The primary analysis time point will be at Week 12.

9.4.2 Statistical model, hypothesis, and method of analysis

For the two primary efficacy variables at each time point (response in skin histology/K16 expression to treatment at Week 12, PASI 90 at Weeks 4, 8, and 12), 95% confidence interval

[redacted]

for the difference between the two treatment groups with respect to the percentage of patients who have the "event" will be calculated using the normal approximation to the binomial distribution.

The primary analysis of the primary efficacy variables will be based on the Full Analysis Set.

9.4.3 Handling of missing values/censoring/discontinuations

For the two primary efficacy variables at Week 12 (and other time points), a patient with a missing assessment will be considered as a non-responder.

9.4.4 Sensitivity analyses

The two primary efficacy variables will be analyzed at each time point for the Full Analysis Set using a logistic regression model with treatment and body weight (<90 kg, ≥90 kg) as explanatory variables (Stokes, Davis, and Koch, 2012). The odds ratios and 95% confidence intervals for the odds ratios based on the fitted model will be reported.

Estimates of differences between the two proportions within each stratum will be calculated and examined for meaningful treatment-by-stratum interaction.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary efficacy objective (i.e., explore the modulation of subcutaneous adipose tissue and skin inflammation from baseline to Week 52) will be assessed using the same two primary efficacy variables, but measured at Week 52.

9.5.2 Safety variables

The assessment of safety will be based mainly on the frequency of adverse events and laboratory data. Other safety data, including vital signs (blood pressure, weight, waist circumference, BMI), and clinical laboratory variables (glucose, insulin, hs-CRP, HOMA-IR, HbA1c) will be summarized by stratum, as appropriate.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (e.g., severity or relatedness to study medication) will be listed, as appropriate.

Adverse events and serious adverse events up to and including Week 12 visit will be included in the database for the analysis at the primary analysis time point (Week 12). All Adverse events and serious adverse events will be included in the final database analysis (Week 53).

Laboratory variables and other safety variables will be summarized, as appropriate.

Analysis of safety data will be based on the Safety Set.

[redacted]

[redacted]

9.7 Interim analyses

The database of this study will be locked twice, first after the end of double-blind treatment period (Week 12) and again at the end of the follow-up period (Week 53). Data analyses will follow each database lock. The main analysis for the primary objective will be done at Week 12. As Week 12 analysis considered primary and no specific hypothesis is pre-identified for testing, adjustment of significance level due to this interim analysis is irrelevant.

In addition, after all patients complete their baseline visit, the demographic and baseline characteristics may be summarized to help design new studies.

[redacted]

9.8 Sample size calculation

The table below considers total sample sizes of 75 patients (50 in secukinumab group and 25 in placebo group) and 99 patients (66 in secukinumab group and 33 in placebo group) to estimate the difference between the two groups with respect to the pooled estimate of the two percentages of patients who have the "event" at Week 12 for each of the two primary efficacy variables. The entries in the table are the "margin of error" (half-width of confidence interval) for a two-sided 95% confidence interval (Julious and Patterson, 2004; Kianifard and Islam, 2011; nQuery Advisor 7.0).

Table 9-1 Sample size calculations for percentage of patients who have the "event"

Percentage with "event"	Half-width of confidence interval for n = 75	Half-width of confidence interval for n = 99
30%	25.0%	21.4%
40%	26.5%	22.7%
50%	27.0%	23.2%
60%	26.5%	22.7%
70%	25.0%	21.4%

Based on the results in the above table, it was decided that approximately 75 randomized patients (50 in secukinumab group and 25 in placebo group) will be randomized in this exploratory study to estimate the difference in response rates between the two treatment groups.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. 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 patient's source documents.

[redacted]

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis or CRO monitor after IRB/IEC approval.

10.3 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, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. 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.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group 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.

11 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 patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an

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investigator allowed to collect additional data or conduct any additional procedures for any research-related purpose involving any investigational drugs under the protocol.

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.

11.1 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 intended to eliminate an apparent immediate hazard to patients 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 patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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13 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. Notable values for blood pressure and pulse are presented in Section 6.7.2.

No specific action is pre-defined within this protocol to respond to specific notable laboratory or vital signs values. It will be decided by the investigator/qualified site staff whether and which specific action needs to be taken to respond to any notable values, taking into account the overall status of the patient.

Liver function and related variables

ALT (SGPT)	> 3 x Upper Limit of Normal (ULN)
AST (SGOT)	> 3 x ULN
Total bilirubin	> 1.5 x ULN
Alkaline phosphatase	> 2 x ULN

Renal function

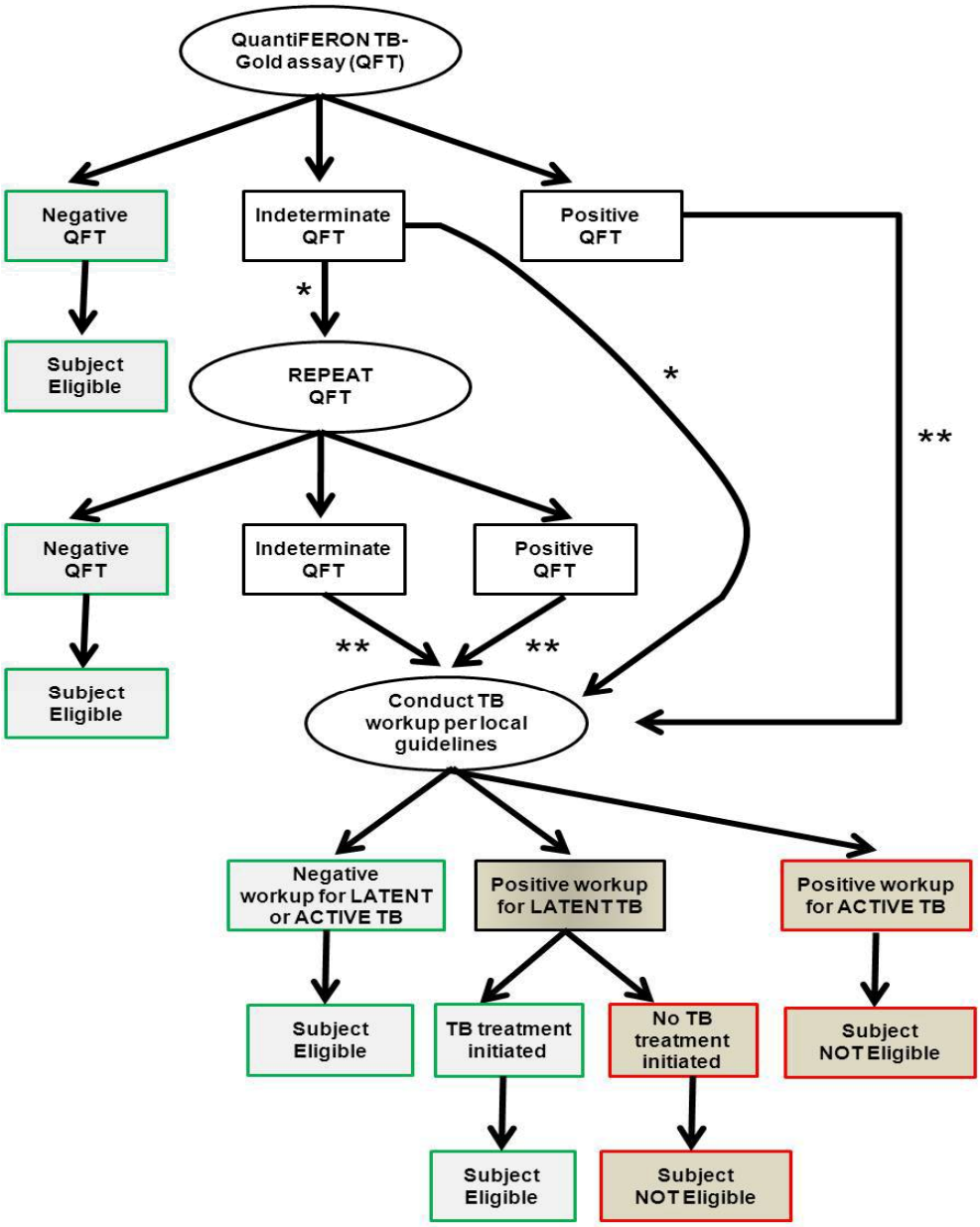
Creatinine (serum)	> 1.5 x ULN

Hematology variables

Hemoglobin	≥ 2.0 g/dL decrease from baseline
Platelet count	< Lower Limit of Normal (LLN)
White blood cell	< 0.8 x LLN
Neutrophils	< 0.9 x LLN
Eosinophils	> 1.1 x ULN
Lymphocytes:	> 1.1 x ULN

[redacted]

14 Appendix 2: Tuberculosis screening flowchart

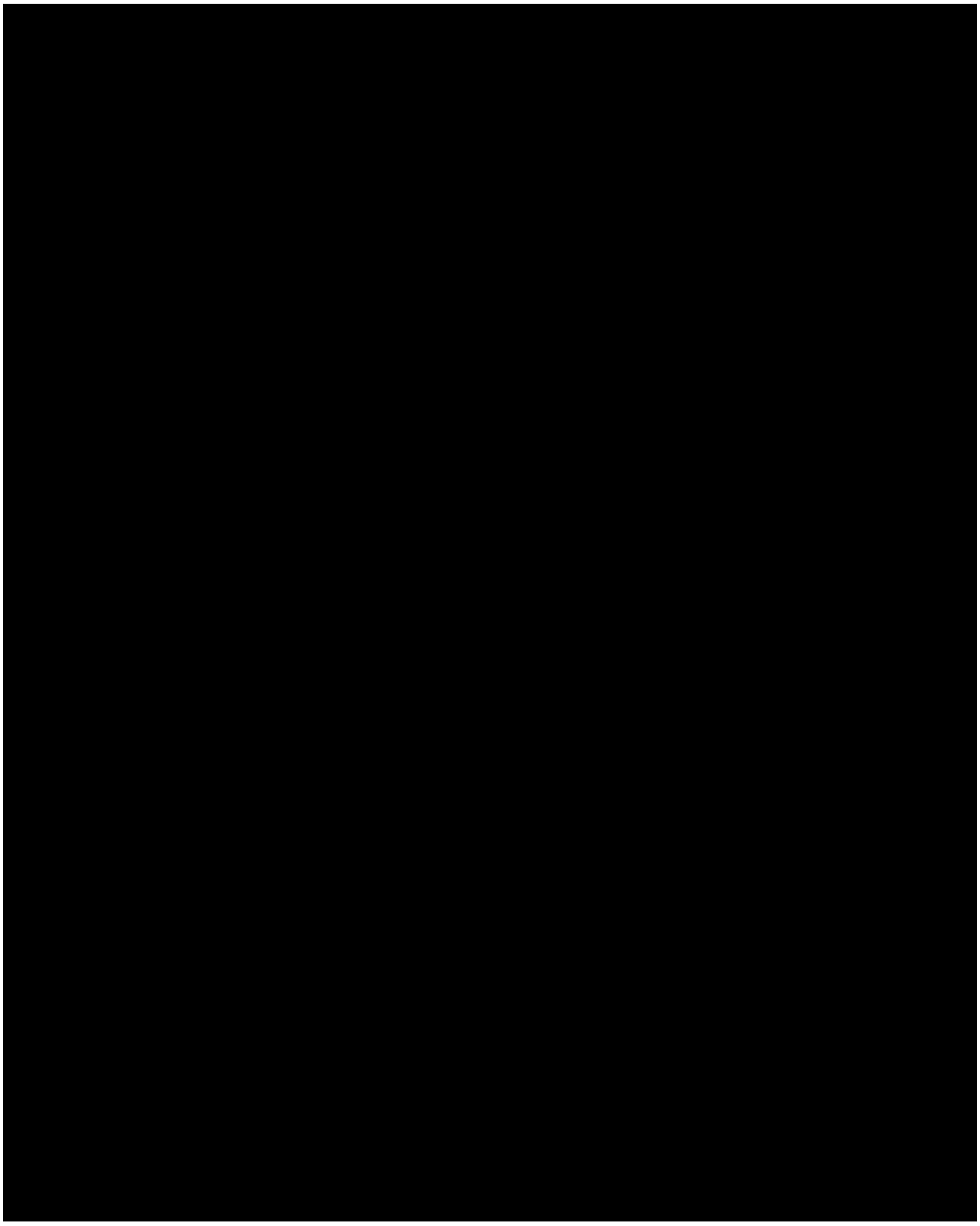


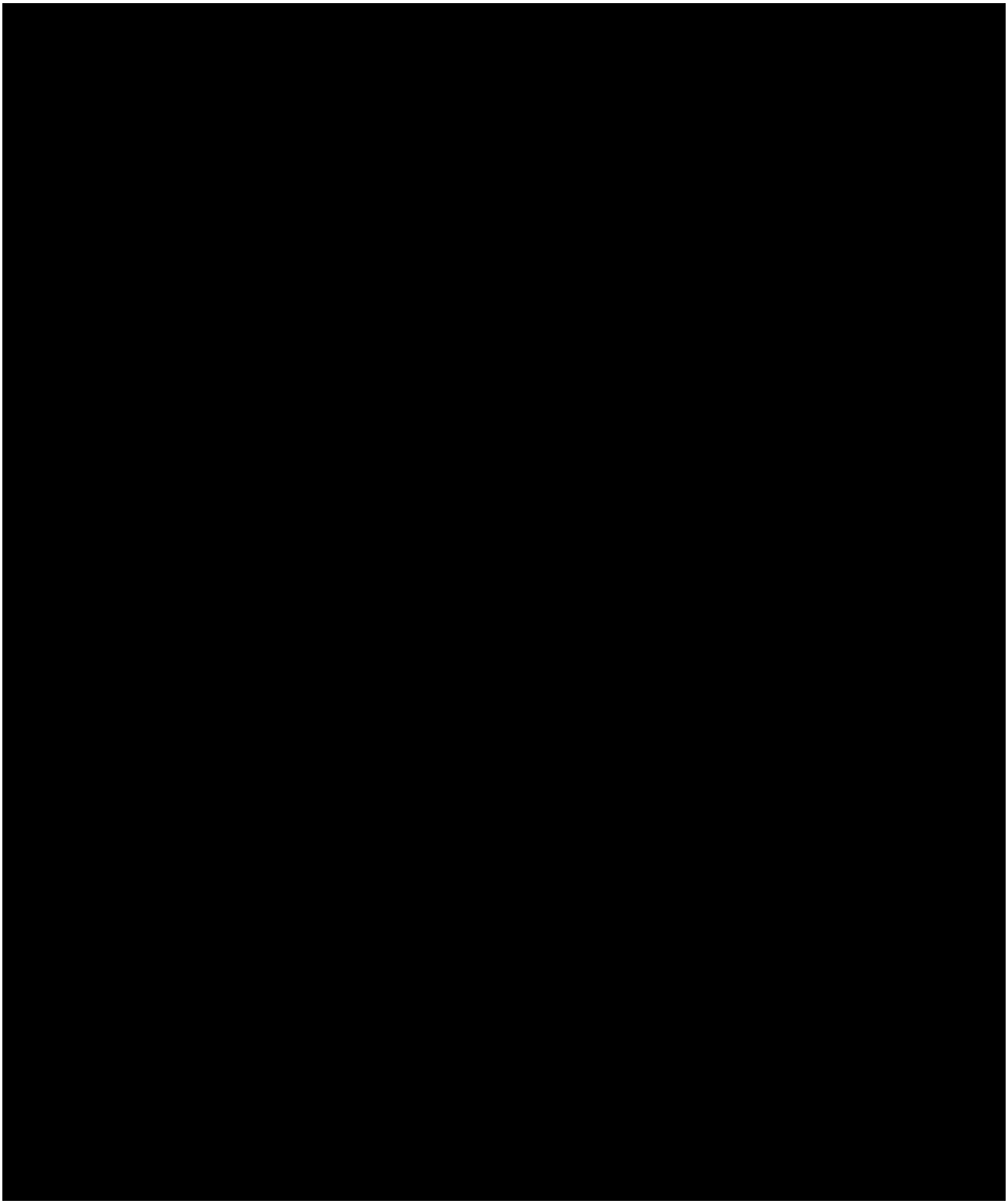
The subject will not be eligible for randomization if "active tuberculosis is present "or if "latent tuberculosis is present and is untreated as per local guidelines."

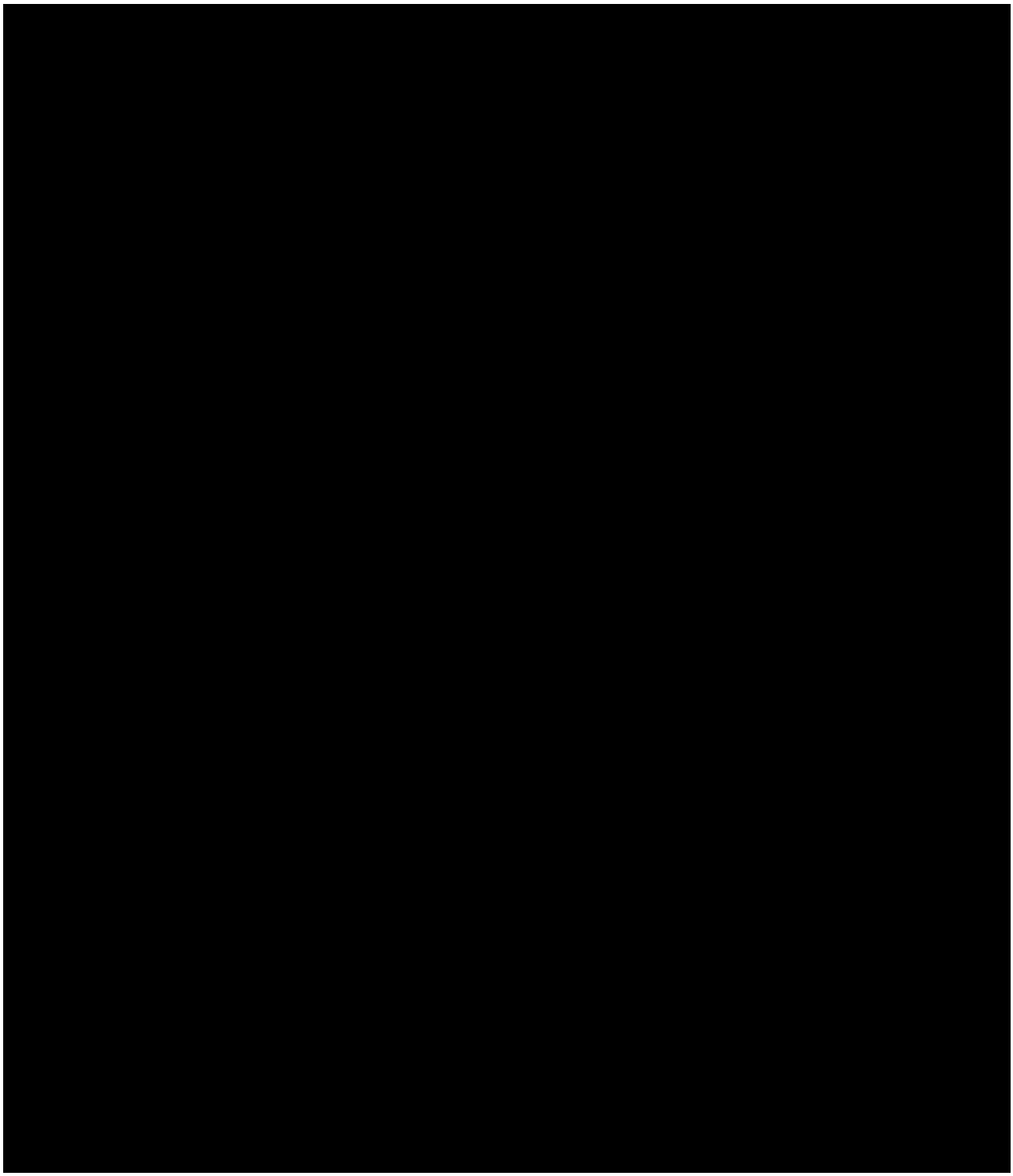
* If the first QuantiFERON® TB-Gold In-Tube test (QFT) is indeterminate, the investigator may choose to perform a second QFT or refer the subject for tuberculosis workup per local guidelines.

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

[redacted]







16 Appendix 4: Psoriasis Area and Severity Index (PASI) and Body Surface Area (BSA)

Body Region	Erythema (E)	Thickening (I) (plaque elevation, induration)	Scaling (D) (desquamation)	True Area % (covered by lesions)
Head and Neck (H)	☐ None (0) ☐ Slight (1) ☐ Moderate (2) ☐ Severe (3) ☐ Very severe (4)	☐ None (0) ☐ Slight (1) ☐ Moderate (2) ☐ Severe (3) ☐ Very severe (4)	☐ None (0) ☐ Slight (1) ☐ Moderate (2) ☐ Severe (3) ☐ Very severe (4)	Record % (0–100) _____ %
Trunk, Axillae and Groin (T)	☐ None (0) ☐ Slight (1) ☐ Moderate (2) ☐ Severe (3) ☐ Very severe (4)	☐ None (0) ☐ Slight (1) ☐ Moderate (2) ☐ Severe (3) ☐ Very severe (4)	☐ None (0) ☐ Slight (1) ☐ Moderate (2) ☐ Severe (3) ☐ Very severe (4)	Record % (0–100) _____ %
Upper Limbs (U)	☐ None (0) ☐ Slight (1) ☐ Moderate (2) ☐ Severe (3) ☐ Very severe (4)	☐ None (0) ☐ Slight (1) ☐ Moderate (2) ☐ Severe (3) ☐ Very severe (4)	☐ None (0) ☐ Slight (1) ☐ Moderate (2) ☐ Severe (3) ☐ Very severe (4)	Record % (0–100) _____ %
Lower Limbs and Buttocks (L)	☐ None (0) ☐ Slight (1) ☐ Moderate (2) ☐ Severe (3) ☐ Very severe (4)	☐ None (0) ☐ Slight (1) ☐ Moderate (2) ☐ Severe (3) ☐ Very severe (4)	☐ None (0) ☐ Slight (1) ☐ Moderate (2) ☐ Severe (3) ☐ Very severe (4)	Record % (0–100) _____ %

[redacted]

17 Appendix 5: Sample Log Table

Sample log time schedule for sampling for [redacted] adipose tissue, [redacted]

[redacted]

Week	Visit No.	Time Point	[redacted]	Blood - Microparticles & Leukocytes (FACS - ambient)	Blood - Microparticles & Leukocytes (FACS - ambient)	Blood - Microparticles & Leukocytes (FACS - frozen)	Blood - Microparticles & Leukocytes (FACS - frozen) Sample #	[redacted]
Screening	1	*Weeks -4 to Baseline*						
Baseline	2	*predose*		10 mL	601	10 mL	605	
Week 1 (Day 8)	3							
Week 2 (Day 15)	4							
Week 3 (Day 22)	5							
Week 4 (Day 29)	6	*predose*						
Week 8 (Day 57)	7							
Week 12 (Day 85)	8	*predose*		10 mL	602	10 mL	606	
Week 13 (Day 92)	9							
Week 16 (Day 113)	10							
Week 24 (Day 169)	11	*predose*		10 mL	603	10 mL	607	
Week 32 (Day 225)	12							
Week 40 (Day 281)	13							
Week 48 (Day 337)	14							
Week 52 (Day 365)	15			10 mL	604	10 mL	608	
Week 53 (Day 372)								
Total mL:				**40**		**40**		
Consolidated total mL:	**147.5**							

[redacted]