NOVARTIS

US Clinical Development and Medical Affairs - General Medicine

AIN457/Secukinumab

Clinical Trial Protocol CAIN457AUS02 / NCT02690701

A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the effect of secukinumab on aortic vascular inflammation and cardiometabolic biomarkers after 12 weeks of treatment, compared to placebo, and up to 52 weeks of treatment with secukinumab in adult subjects with moderate to severe chronic plaque-type psoriasis

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List of abbreviations

AE	adverse event
ALT (SGPT)	alanine aminotransferase
ANCOVA	Analysis of covariance
AST (SGOT)	aspartate aminotransferase
BSA	Body Surface Area
CFR	US Code of Federal Regulations
eCRF	electronic Case Report Form
CRO	Contract Research Organization
CV	cardiovascular
DICOM	Digital Imaging and Communication in Medicine
DLQI	Dermatology Life Quality Index
DS&E	Drug Safety & Epidemiology
DSM	Drug Supply Management
EDC	Electronic Data Capture
FDG-PET/CT	[18F]-fluorodeoxyglucose positron emission tomography with computer assisted tomography
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HRQoL	Health-related Quality of Life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for Use (secukinumab)
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011

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IL	Interleukin
IMT	intima-media thickness
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
LOCF	Last-observation-carried-forward
MedDRA	Medical dictionary for regulatory activities
MRI	magnetic resonance imaging
MTX	methotrexate
OC/RDC	Oracle Clinical/Remote Data Capture
OTC	over-the-counter
PASI	Psoriasis Area and Severity Index
PFS	prefilled syringe
PUVA	psoralen ultraviolet A
SAE	serious adverse event
s.c.	subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reactions
SUV	standardized uptake value
TB	tuberculosis
TBR	target to background ratio
TCS	topical corticosteroids
ULN	upper limit of normal
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
WBC	white blood cells
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Period	A portion of the study which serves a specific purpose. Typical periods are: screening/recruitment, wash-out, treatment, and follow-up
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study 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.”
Study treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
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

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Amendment 3

Rationale for amendment

The purpose of Amendment 3 is to revise the list of cardiometabolic biomarkers under investigation in this study. The following sections have been updated to reflect the correct cardiometabolic biomarkers:

- Protocol Summary
- Section 2.2
- Section 6.4
- Section 6.4.2

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

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

[redacted]

Protocol summary

Protocol number	CAIN457AUS02
Title	A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the effect of secukinumab on aortic vascular inflammation and cardiometabolic biomarkers after 12 weeks of treatment, compared to placebo, and up to 52 weeks of treatment with secukinumab in adult subjects with moderate to severe chronic plaque-type psoriasis
Brief title	Study to evaluate the effect of secukinumab compared to placebo on aortic vascular inflammation in subjects with moderate to severe plaque psoriasis
Sponsor and Clinical Phase	Novartis / Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Secukinumab targets Interleukin 17a (IL-17a), which is increasingly understood to be a critical component of the pathophysiology of psoriasis, and evolving research also suggests that IL-17 may promote cardiovascular disease. This study will provide a comparison of secukinumab to placebo with respect to aortic vascular inflammation at 12 weeks of treatment, and up to 52 weeks of treatment in subjects with moderate to severe plaque psoriasis.
Primary Objective(s)	To evaluate the effect of secukinumab compared to placebo on aortic vascular inflammation with respect to the change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio from the aorta
Secondary Objectives	• To evaluate the effect of secukinumab compared to placebo with respect to change from baseline in cardiometabolic biomarkers (cardiometabolic function [lipid particle size, HDL function (cholesterol efflux)], measures of inflammation [TNF-Alpha, IL-6, C-reactive protein, GlycA], adiposity [leptin and adiponectin], insulin resistance [insulin levels/glucose to yield HOMA-IR], and markers predictive of diabetes [apolipoprotein B, ferritin, IL-2 receptor A, IL-18, and fetuin-A]) at Week 12 • To evaluate the effect of secukinumab compared to placebo in subjects with moderate to severe chronic plaque-type psoriasis with respect to change from baseline in the PASI 75, 90 and 100 response rates at Week 12 • To evaluate the effect of secukinumab compared to placebo in subjects with moderate to severe chronic plaque-type psoriasis with respect to the Investigator's Global Assessment mod 2011 (IGA mod 2011) 0 or 1 response at Week 12

	• To evaluate the effects of secukinumab compared to placebo with respect to change from baseline in the Dermatology Life Quality Index (DLQI) total score at Week 12 • To evaluate the clinical safety and tolerability of secukinumab as assessed by vital signs, clinical laboratory variables, and adverse event monitoring
Study design	This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study in approximately 84 subjects with moderate to severe plaque psoriasis. The study consists of four periods: Screening (from 1 to 4 weeks); Double-blind Treatment Period (12 weeks); Double-blind Induction Period (4 weeks); and Open-label Treatment Period (36 weeks). At Visit 2, eligible subjects will be randomized in a 1:1 ratio to one of two treatment groups – secukinumab or placebo. At the end of the Double-blind Treatment Period, all subjects receiving placebo will be switched to secukinumab treatment for the remainder of the study.
Population	The study population will consist of male and female subjects at least 18 years of age with moderate to severe plaque-type psoriasis who are candidates for systemic therapy or phototherapy.
Inclusion criteria	• Provide written, signed and dated informed consent before any study-related activity is performed; where relevant, a legal representative will also sign the informed study consent according to local laws and regulations • Males and females ≥18 years of age at time of screening • Clinical diagnosis of chronic plaque-type psoriasis at least 6 months prior to randomization as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by the Investigator • Moderate to severe plaque psoriasis as defined at Baseline by: o ≥10% Body Surface Area (BSA) involvement **and** o PASI score of ≥12 **and** o IGA mod 2011 score of ≥3 (based on a scale of 0 – 4) • Candidate for systemic therapy, defined as having plaque psoriasis inadequately controlled by: o topical treatment and/or o phototherapy and/or o previous systemic therapy • Physical examination and FDG-PET/CT scan without clinically significant findings that would meaningfully alter the risk-benefit profile of secukinumab in the Investigator's opinion, and clinical laboratory results within laboratory reference ranges, or abnormal results that are deemed to be not clinically significant by the Investigator

Exclusion criteria	• Forms of diagnosed psoriasis other than chronic plaque psoriasis (e.g., erythrodermic, generalized or localized pustular psoriasis, or new onset guttate psoriasis) • Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17RA receptors (e.g., ixekizumab, or brodalumab) • 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 • Ongoing use of prohibited psoriasis treatments (e.g., topical or systemic corticosteroids, other topical medications, systemic psoriasis treatments oral or biological, UV therapy) • Women of child-bearing potential not using effective methods of contraception, pregnant or nursing women • Positive serology for human immunodeficiency virus (HIV), hepatitis B or C infection, or known history of other severe, recurrent or persistent infections • Any underlying condition which significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy • History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection • Plans for administration of live vaccines during the study period or 6 weeks before randomization
Study drug and control drug	Study drug: • Secukinumab, liquid formulation in a prefilled syringe (PFS) for subcutaneous injection Control drug: • Placebo to secukinumab, liquid formulation in a prefilled syringe (PFS) for subcutaneous injection
Efficacy assessments	• Target (arterial vascular uptake) to background (venous blood pool) ratio from the aorta as measured by FDG-PET/CT • Cardiometabolic biomarkers: (cardiometabolic function [lipid particle size, HDL function (cholesterol efflux)], measures of inflammation [TNF-Alpha, IL-6, C-reactive protein, GlycA], adiposity [leptin and adiponectin], insulin resistance [insulin levels/glucose to yield HOMA-IR], and markers predictive of diabetes [apolipoprotein B, ferritin, IL-2 receptor A, IL-18, and fetuin-A]) • PASI: Psoriasis Area and Severity Index • IGA mod 2011: Investigator's Global Assessment modified 2011

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	• DLQI: Dermatology Life Quality Index
Safety assessments	• Adverse events and serious adverse events • Laboratory assessments (e.g., hematology, clinical chemistry, viral serology, serum and urine pregnancy) • Vital signs, 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 subjects will be available for analysis. Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05. The following analysis sets will be used for the statistical reporting and analyses: Randomized Set: The randomized set includes all subjects who were randomized. Safety Set: The Safety Set includes all subjects who received at least one dose of study medication. Subjects will be analyzed according to treatment received. Full Analysis Set: The Full Analysis Set includes all subjects to whom study medication has been assigned. Subjects inappropriately randomized (e.g., IRT was called in error for randomization of a screen failed subject) will be excluded from this analysis set. Data will be summarized with respect to demographic and baseline characteristics 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. The primary efficacy variable is the change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio from the aorta. Target to background ratio is considered the standard reporting variable based on FDG-PET/CT scans in vascular studies (see Section 6.4.1). The primary analysis time point will be at Week 12. The primary efficacy variable will be analyzed by an analysis of covariance (ANCOVA) model with treatment, baseline, and body weight (<90 kg, ≥90 kg) as explanatory variables. The least squares means of the two treatment groups, least squares mean difference of the treatment groups, 95% confidence interval for the difference in the two treatment groups, and p-value based on the fitted linear model will be reported. Missing data will be imputed using the last-observation-carried-forward (LOCF) method. If a subject has no post-baseline value, the missing value will not be imputed and the subject will be removed from the

	analysis. A supportive nonparametric analysis will be performed to examine the consistency of results if the assumption of normality for the distribution of the primary efficacy variable is not tenable. For this supportive analysis, the primary efficacy variable will be analyzed using the stratified Wilcoxon rank-sum test with modified ridit scores (van Elteren's test), adjusting for body weight (<90 kg, ≥90 kg) (Stokes, Davis, and Koch, 2012). The primary analysis and supporting analysis of the primary efficacy variable will be based on the Full Analysis Set. The secondary efficacy variables are the following: • Change from baseline in each biomarker (see Section 6.4) • PASI 75 response (yes, no) • PASI 90 response (yes, no) • PASI 100 response (yes, no) • IGA mod 2011 score of 0 or 1 (yes, no) • Change from baseline in DLQI total score Change from baseline in each biomarker and change from baseline in DLQI total score will be analyzed at each time point using the same ANCOVA model as for the primary efficacy variable, and missing data will be imputed using the LOCF method. IGA mod 2011 score of 0 or 1 and PASI 75 / 90 / 100 responses will be analyzed at each time point using the Cochran-Mantel-Haenszel test to compare secukinumab and placebo, adjusting for body weight (<90 kg, ≥90 kg) (Stokes, Davis, and Koch, 2012). A 95% confidence interval for the difference between the two treatment groups in the proportion of subjects who are responders will be calculated using the normal approximation to the binomial distribution. For response (yes, no) at Week 12 (and other time points), a subject with a missing assessment will be considered as a responder (yes) if the subject meets the response criterion at the time of premature discontinuation from the study. Otherwise, the subject will be considered as a non-responder (no). Analyses of the secondary efficacy variables will be based on the Full Analysis Set. The assessment of safety will be based mainly on the frequency of adverse events and laboratory data. Other safety data (e.g., vital signs and special tests) will be considered, as appropriate. Analysis of safety data will be based on the Safety Set. The sample size was based on change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio (TBR) from the aorta. Using a t-test, a clinically important mean treatment difference of 0.15, a (common) standard deviation (SD) of 0.196, an allocation ratio of 1:1, a two-sided significance level of 0.05, and a power of 0.90, it was determined that approximately 74 subjects (37 in each

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	treatment group) are necessary (nQuery Advisor 7.0) (Bissonnette et al 2013; Tawakol et al 2013). Without adjusting for multiplicity, the sample size of 74 subjects will also provide at least 0.90 power for other biomarkers (see Section 6.4.2) if the treatment difference is 0.76 SD or smaller. The general threshold for clinical importance is 1 SD. Allowing for a loss to follow-up rate of 0.10, approximately 84 subjects (42 in each treatment group) will be randomized.
Key words	Plaque psoriasis, vascular inflammation, secukinumab, biologic, monoclonal antibody

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1 Introduction

1.1 Background

Psoriasis is a chronic, immune-mediated, inflammatory skin condition characterized by exacerbations and remissions. It is estimated to affect approximately 2% of the US population (National Psoriasis Foundation 2014).

Psoriasis is associated with defects in high-density lipoprotein (HDL) function, insulin resistance, and increased aortic vascular inflammation as measured by [18F]-fluorodeoxyglucose positron emission tomography with computer assisted tomography (FDG-PET/CT). These changes found in FDG-PET/CT would be the equivalent to a decade of aging in an individual without psoriasis (Mehta et al 2011). Patients with moderate to severe psoriasis have an increased risk of myocardial infarction, stroke, and cardiovascular (CV) death independent of traditional risk factors (Gelfand et al 2006; Gelfand et al 2009; Mehta et al 2010; Ogdie et al 2015). Observational data suggest that immune modulation with methotrexate or TNF inhibitors can lower the risk of major cardiovascular events in this at-risk population (Roubille et al 2015).

Interleukin 17a (IL-17a; also known as IL-17) is increasingly understood to be a critical component of the pathophysiology of psoriasis and evolving literature suggests that IL-17 may also promote cardiovascular disease (Abbas et al 2015; Erbel et al 2014; Karbach et al 2014).

Secukinumab is a recombinant high-affinity fully human monoclonal anti-human IL-17A antibody of the immunoglobulin (Ig) G1/κ-class. Secukinumab binds to human IL-17A and neutralizes the bioactivity of this cytokine. Secukinumab has demonstrated efficacy in reducing psoriasis skin severity. Psoriasis skin severity directly relates to vascular inflammation and cardiovascular comorbidity (Naik et al 2015; Yeung et al 2013). Moreover, IL-17 has been shown to activate endothelial cells, promote platelet aggregation and associate with activated neutrophils, therefore, blockade of this pathway would benefit these key aspects of atherogenesis (Erbel et al 2011).

As it has been demonstrated that psoriasis is an independent risk factor for myocardial infarction, cutting edge approaches have since been developed to measure the impact of psoriasis on pathways known to be causally related to vascular events (e.g., HDL function, aortic vascular inflammation). For example, the primary outcome for this study is aortic vascular inflammation as measured by FDG-PET/CT which allows for the anatomical localization and measurement of CD68+ macrophage metabolic activity.

Vascular inflammation is quantified using target to background ratio (TBR) which measures the PET signal in the aorta relative to background (i.e., venous blood pool) and is a widely used metric. Aortic inflammation measured by FDG-PET/CT is reliable (operator independent) (Mehta et al 2012), strongly predictive of future cardiovascular events (Figueroa et al 2013), and is highly sensitive to changes from risk factor modification (statins) (Tawakol et al 2013) to therapeutic lifestyle changes (Lee et al 2008) known to lower the risk of cardiovascular events.

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Therefore, FDG-PET/CT represents an important method of measuring cardiovascular disease and risk.

1.2 Purpose

The purpose of this study is to evaluate the effect of secukinumab compared to placebo on aortic vascular inflammation in subjects with moderate to severe plaque psoriasis. In addition, this study will evaluate the effect of longer-term treatment with secukinumab (up to 52 weeks) on aortic vascular inflammation.

2 Study objectives

2.1 Primary objective(s)

The primary objective is to evaluate the effect of secukinumab 300 mg s.c. compared to placebo on aortic vascular inflammation with respect to the change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio from the aorta. The primary analysis time point will be at Week 12.

2.2 Secondary objectives

- To evaluate the effect of secukinumab compared to placebo with respect to change from baseline in cardiometabolic biomarkers (cardiometabolic function [lipid particle size, HDL function (cholesterol efflux)], measures of inflammation [TNF-Alpha, IL-6, C-reactive protein, GlycA], adiposity [leptin and adiponectin], insulin resistance [insulin levels/glucose to yield HOMA-IR], and markers predictive of diabetes [apolipoprotein B, ferritin, IL-2 receptor A, IL-18, and fetuin-A]) at Week 12
- To evaluate the effect of secukinumab compared to placebo in subjects with moderate to severe chronic plaque-type psoriasis with respect to change from baseline in the PASI 75, 90 and 100 response rates at Week 12
- To evaluate the effect of secukinumab compared to placebo in subjects with moderate to severe chronic plaque-type psoriasis with respect to the Investigator's Global Assessment mod 2011 (IGA mod 2011) 0 or 1 response at Week 12
- To evaluate the effects of secukinumab compared to placebo with respect to change from baseline in the Dermatology Life Quality Index (DLQI) total score at Week 12
- To evaluate the clinical safety and tolerability of secukinumab as assessed by vital signs, clinical laboratory variables, and adverse event monitoring

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3 Investigational plan

3.1 Study design

This study uses a randomized, double-blind, placebo-controlled, parallel-group, multicenter design. Approximately 84 subjects with moderate to severe chronic plaque-type psoriasis will be randomized from approximately 10 investigative sites in the United States.

The study consists of four periods: Screening (from 1 to 4 weeks); Double-blind Treatment Period (12 weeks); Double-blind Induction Period (4 weeks); and Open-label Treatment Period (36 weeks). A schematic of the study design and visits is presented in Figure 3-1, while a detailed visit and assessment schedule can be found in Table 6-1.

Safety, efficacy and patient-reported outcome (PRO) assessments will be performed according to the visit schedule (Table 6-1).

All doses of study treatment will be self-administered. **Self-administration of the study treatment refers to subject self-injection or injection by a trained caregiver regardless of whether self-administration occurs at the study site or at home**. Instruction and training will be provided by site staff to subjects prior to self-injection.

3.1.1 Screening period (Screening to randomization)

The duration of the screening period will be up to four weeks (28 days). Screening will be used to assess subject eligibility and to taper subjects off prohibited medications and treatments.

3.1.1.1 Visit 2 (Baseline)

Visit 2/Baseline should take place once all screening activities have been performed, and all results have been received and are confirmed to be within acceptable ranges for the subject to continue in the study. The Baseline visit should occur no later than 28 days after the initiation of screening.

At Visit 2, all Visit 2/Baseline assessments indicated in Table 6-1 should be performed with the exception of subject randomization via IRT and subject self-administration of study treatment. **Subjects must not be randomized until the clinical reading scan report from the FDG-PET/CT has been received and reviewed to ensure there are no clinically important findings that would preclude a subject from continuing in the study.** Because the receipt of

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the report may take up to 24 hours, the Baseline visit is allowed to occur over a two-day period (+1 additional day if needed).

Once the scan report is reviewed and no clinically important findings are identified, the site should then proceed immediately with subject randomization via IRT and administration of the initial dose of study treatment.

If the FDG-PET/CT scan report does contain clinically important findings, consultation with the Medical Monitor/appropriate medical experts and additional testing/work-up may be required to determine if the subject is eligible to continue in the study or must be discontinued. In these cases, a +7-day window after the completion of the FDG-PET/CT scan is allowed to randomize and administer the first dose of study treatment.

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

The Double-blind Treatment Period is defined as Randomization through Week 12 (prior to the Week 12 dose).

At the start of the Double-blind Treatment Period, eligible subjects will be randomized via Interactive Response Technology (IRT) in a 1:1 ratio to one of two treatment groups (secukinumab 300 mg or placebo). **Subjects must be randomized and receive their first dose of study treatment no later than 7 days after the FDG-PET/CT scan.**

- **Secukinumab**: secukinumab 300 mg (two s.c. injections of the secukinumab 150 mg dose) once weekly for five weeks (at Randomization, Weeks 1, 2, 3, and 4) followed by a dose after four weeks at Week 8 (last dose during Double-blind Treatment Period).
- **Placebo**: placebo (two s.c. injections of 150 mg secukinumab placebo per dose) once per week for five weeks (at Randomization, Weeks 1, 2, 3 and 4) followed by a dose after four weeks at Week 8 (last dose during Double-blind Treatment Period).

During the Double-blind Treatment Period, all subjects will attend study visits at Randomization, Weeks 1, 2, 3, 4, 8, and 12, and all doses of study treatment will be **self-administered at the study site**.

Assessments for the primary efficacy variable will be performed at Week 12 for both treatment groups **prior to** subjects receiving their Week 12 dose.

All subjects who discontinue study treatment prematurely for any reason before the end of Double-blind Treatment Period should return to the study site for the performance of the Visit 8/Week 12 End of Treatment 1 (EOT1) assessments. The EOT1 visit should be scheduled 28 days (± 7 days) after the last dose of study treatment.

3.1.2.1 Visit 8 (Week 12)

At Visit 8, all Visit 8/Week 12 assessments indicated in Table 6-1 should be performed with the exception of subject self-administration of the Week 12 dose and dispensation of the study treatment for the at-home dosing at Weeks 13, 14, and 15. **Subjects must not self-administer**

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the Week 12 dose of study treatment until the clinical reading scan report from the FDG-PET/CT has been received and reviewed to ensure there are no clinically important findings that would preclude a subject from continuing in the study. Because the receipt of the report may take up to 24 hours, Visit 8/Week 12 is allowed to occur over a two-day period (+1 additional day if needed).

Once the scan report is reviewed and no clinically important findings are identified, the site should then proceed immediately with subject administration of the Week 12 dose and dispensation of the study treatment for the Weeks 13, 14, and 15 at-home dosing.

If the FDG-PET/CT scan report does contain clinically important findings, consultation with the Medical Monitor/other appropriate medical experts, and additional testing/work-up may be required to determine if the subject is eligible to continue in the study or must be discontinued. In these cases, a +7-day window after the completion of the FDG-PET/CT scan is allowed for the subject to administer the Week 12 dose.

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

All subjects who complete the Double-blind Treatment Period will enter the Double-blind Induction Period.

During the Double-blind Induction Period, subjects randomized to placebo during the Double-blind Treatment Period will be switched over to treatment with secukinumab 300 mg. The Double-blind Induction Period is defined as the Week 12 dose through the Week 15 dose. **Subjects must administer the Week 12 dose no later than 7 days after the Week 12 FDG-PET/CT scan.**

- **Secukinumab**: Subjects who were randomized to the secukinumab treatment group at Visit 2/Baseline will continue to self-administer secukinumab 300 mg (two s.c. injections of the 150 mg dose) at Week 12. In order to maintain the blind, these subjects will undergo a sham induction with weekly placebo injections at Weeks 13, 14, and 15.
- **Placebo**: Subjects who were randomized to the placebo treatment group at Visit 2/Baseline will begin to self-administer secukinumab 300 mg (two s.c. injections of the secukinumab 150 mg dose) weekly for four weeks at Weeks 12, 13, 14, and 15.

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

All subjects who discontinue study treatment prematurely for any reason before the end of Double-blind Induction Period should return to the study site for the performance of the Visit 14/Week 52 End of Treatment 2 (EOT2) assessments. The EOT2 visit should be scheduled 28 days (± 7 days) after the last dose of study treatment.

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

All subjects 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 subjects in

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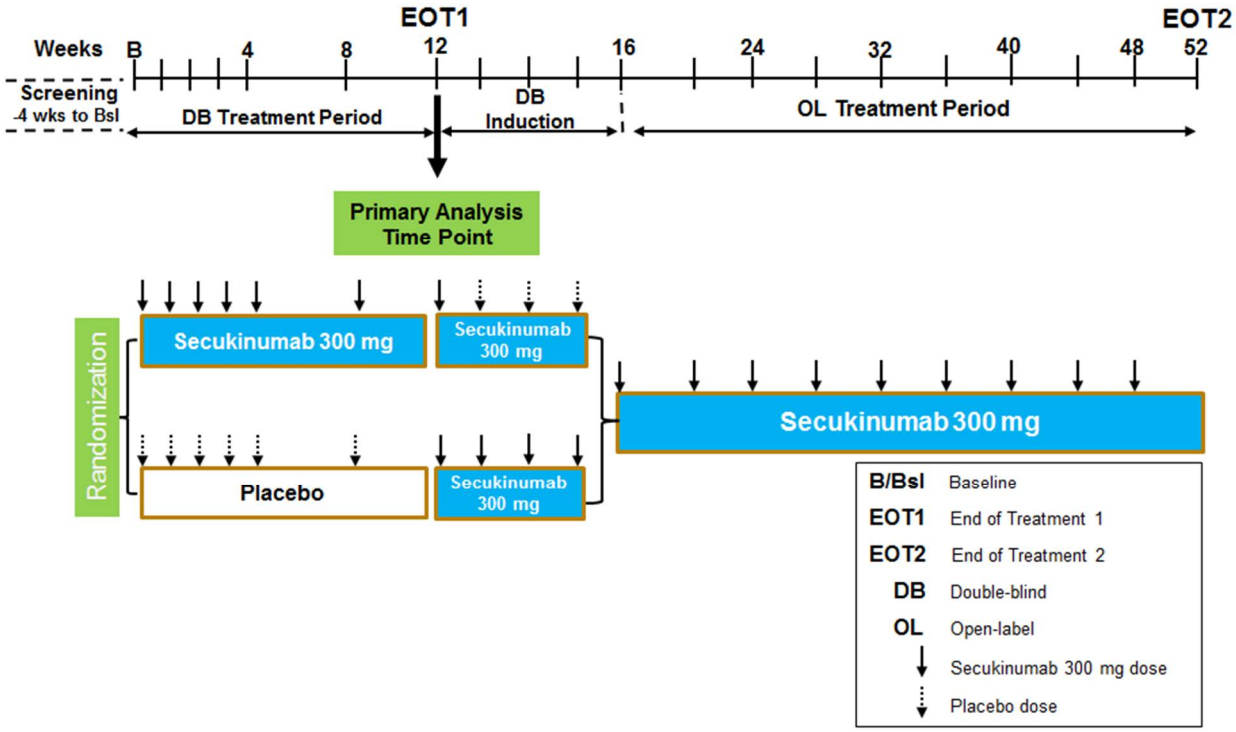
the Open-label Treatment Period will receive secukinumab 300 mg s.c. at four-week intervals beginning at Week 16 through Week 48 (last dose during the Open-Label Treatment Period).

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.

All subjects who discontinue study treatment 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 14/Week 52 End of Treatment 2 (EOT2) assessments. The EOT2 visit should be scheduled 28 days (± 7 days) after the last dose of study treatment.

Figure 3-1 Study design



3.2 Rationale of 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 subjects 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. However, as the study design provides for treatment duration of up to 52 weeks, it also allows for the assessment of longer-term safety and tolerability of secukinumab in this population. For subjects randomized to receive placebo at Visit 2/Baseline, the 52-week treatment duration allows these subjects the opportunity to receive up to 40 weeks of treatment with secukinumab.

Patients with moderate to severe psoriasis have a clinically significant increased risk of major cardiovascular events and mortality independent of traditional risk factors. Treatments that improve not only the skin manifestations of psoriasis but also its cardiovascular co-morbidities are of intense clinical and scientific interest. Measurement of aortic inflammation by FDG-PET/CT is a reproducible, operator independent, prognostic marker of future vascular events (Figueroa et al 2013; Mehta et al 2012). Furthermore, it responds to statins and modulates in a short time frame (i.e., within 12 weeks) unlike alternative approaches such as carotid intima-media thickness (IMT) and MRI-based measures of wall thickness (Tawakol et al 2013).

3.3 Rationale of 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 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 subjects 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.

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.

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,

[redacted]

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 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

[redacted]

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 and 2 are presented in Table 3-1.

Table 3-1 Clinical outcomes at Week 12 in adults with plaque psoriasis in Trials 1 and 2

	Trial 1			Trial 2		
	Secukinumab **300 mg (N=245) n (%)**	Secukinumab **150 mg (N=245) n (%)**	**Placebo (N=248) n (%)**	**Secukinumab 300 mg (N=327) n (%)**	**Secukinumab 150 mg (N=327) n (%)**	**Placebo (N=326) n (%)**
PASI 75 response	200 (82)	174 (71)	11 (4)	249 (76)	219 (67)	16 (5)
IGA of clear or almost clear	160 (65)	125 (51)	6 (2)	202 (62)	167 (51)	9 (3)

The results of Trials 3 and 4 are presented in Table 3-2.

Table 3-2 Clinical outcomes at Week 12 in adults with plaque psoriasis in Trials 3 and 4

	Trial 3			Trial 4		
	Secukinumab **300 mg (N=59) n (%)**	Secukinumab **150 mg (N=59) n (%)**	**Placebo (N=59) n (%)**	**Secukinumab 300 mg (N=60) n (%)**	**Secukinumab 150 mg (N=61) n (%)**	**Placebo (N=61) n (%)**
PASI 75 response	44 (75)	41 (69)	0 (0)	52 (87)	43 (70)	2 (3)
IGA of clear or almost clear	40 (68)	31 (53)	0 (0)	44 (73)	32 (52)	0 (0)

Examination of age, gender, and race subgroups did not identify differences in response to secukinumab among these subgroups. Based on post-hoc sub-group analyses in subjects with moderate to severe psoriasis, subjects with lower body weight and lower disease severity may achieve an acceptable response with secukinumab 150 mg.

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 and in 72% (126/174) of subjects treated with secukinumab 150 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 and in 59% (74/125) of subjects treated with secukinumab 150 mg. Similarly in Trial 2, PASI 75 responders maintained their responses in 84% (210/249) of subjects treated with secukinumab 300 mg and in 82% (180/219) of subjects treated with secukinumab 150 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 and in 68% (113/167) of subjects treated with secukinumab 150 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©.

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, 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. 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.

Pre-treatment evaluation of 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 subjects with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Subjects receiving secukinumab should be monitored closely for signs and symptoms of active TB during and after treatment.

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.

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.

[redacted]

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.

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.

In summary, the expected overall safety profile of secukinumab from a mechanism of action perspective is anticipated to be comparable to, or better than, that of other approved cytokine targeting therapies.

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

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. It is therefore considered appropriate to initiate this study. It is unclear if there is an additional benefit for vascular inflammation in psoriasis subjects, and therefore, this study is being conducted to evaluate this question.

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

4 Population

The study population will consist of male and female subjects at least 18 years of age with moderate to severe chronic plaque psoriasis that requires systemic therapy as defined by 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 approximately 84 subjects in approximately 10 centers in the United States. Assuming a 20% screen failure rate, 105 subjects will need to be screened to provide the targeted number of randomized subjects.

Subjects who drop out after they have been randomized will not be replaced.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study have to fulfill all of the following criteria:

[redacted]

1. Provide written, signed and dated informed consent before any study-related activity is performed; where relevant, a legal representative will also sign the informed study consent according to local laws and regulations
2. Males and females ≥18 years of age at time of screening
3. Clinical diagnosis of chronic plaque-type psoriasis at least 6 months prior to randomization as determined by subject interview of his/her medical history and 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 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 plaque psoriasis inadequately controlled by:
   - topical treatment and/or
   - phototherapy and/or
   - previous systemic therapy
6. Physical examination and FDG-PET/CT scan without clinically significant findings that would meaningfully alter the risk-benefit profile of secukinumab in the Investigator's opinion, and clinical laboratory results within laboratory reference ranges, or abnormal results that are deemed to be not clinically significant by the Investigator, in consultation with the Medical Monitor, and noted in the source documents

4.2 Exclusion criteria

Subjects 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 subjects.

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. Subjects not willing to limit UV light exposure (e.g., sunbathing and/or use of tanning devices) during the course of the study

[redacted]

6. Ongoing use of prohibited psoriasis treatments (e.g., topical or systemic corticosteroids, other topical medications, systemic psoriasis treatments oral or biological, UV therapy); washout periods detailed in the protocol must be followed (Table 5-2)
7. Use of any investigational drug within 4 weeks prior to Randomization, or within a period of 5 half-lives of the investigational treatment prior to Randomization, whichever is longer
8. Subjects using cholesterol-lowering medication (e.g., statins) and not on a stable dose for at least 90 days prior to randomization and unable to remain on a stable dose for the duration of the study
9. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test
10. 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 treatment. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) 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 m prior to screening); for female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
    - Use of oral, 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
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 12 weeks 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) or tubal ligation at least 6 weeks ago. In 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

[redacted]

11. Current severe progressive or uncontrolled disease which in the judgment of the Investigator renders the patient unsuitable for the trial or puts the subject at increased risk (e.g., uncontrolled diabetes as evidenced by hemoglobin A1c ≥7%, myocardial infarction within 6 months prior to screening, unstable ischemic heart disease, cerebrovascular accident)
12. Significant medical problems, including but not limited to the following: uncontrolled hypertension with measured systolic ≥180 mmHg and/or diastolic ≥95 mmHg, congestive heart failure (New York Heart Association [NYHA] status of class III or IV
13. Serum creatinine level >2.0 mg/dL (>176.8 µmol/L) or fasting blood glucose ≥150 mg/dL or hemoglobin A1c ≥7% at screening
14. 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
15. 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)
16. 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. Subjects with a positive QFT test may participate in the study if a full tuberculosis work up (according to local practice/guidelines) completed within 12 weeks prior to randomization establishes conclusively that the subject 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
17. Positive serology for human immunodeficiency virus (HIV), hepatitis B or C infection, or known history of other severe, recurrent or persistent infections
18. 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 subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy
19. Active systemic infections during the 2 weeks prior to randomization (exception: common cold) or any infection that reoccurs on a regular basis
20. Plans for administration of live vaccines during the study period or 6 weeks before randomization
21. Any medical or psychiatric condition which, in the Investigator's opinion, would preclude the subject from adhering to the protocol or completing the study per protocol
22. History or evidence of ongoing substance abuse within 12 months prior to screening, or not willing to limit alcohol use to ≤14 drinks per week within 4 weeks prior to Baseline and throughout the duration of the study
23. History of hypersensitivity to constituents of the study treatment and/or subjects who are allergic to rubber or latex (the needle cap of the single-use prefilled syringe for secukinumab

[redacted]

and placebo may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals)

24. Subjects 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 Protocol requested treatment

5.1.1 Study treatment

The following study treatments will be used:

- **Study drug**
  - Secukinumab 150 mg; 1 ml liquid formulation in a single-use prefilled syringe (PFS)
- **Control drug**
  - Placebo to secukinumab 150 mg; 1 ml liquid formulation in a single-use prefilled syringe (PFS)

Study drug: secukinumab 300 mg

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

Control drug: placebo

Placebo to secukinumab 150 mg for s.c. injection is provided in a matching prefilled syringe (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.

Secukinumab 150 mg prefilled syringes and placebo prefilled syringes will be supplied by Novartis.

All study treatments will be labeled appropriately.

5.1.2 Additional study treatment

No additional treatment beyond study treatment is requested for this trial.

5.2 Treatment groups

At Visit 2/Baseline, eligible subjects will be randomized to one of the following two treatment groups in a ratio of 1:1, with approximately 42 subjects per group:

1. **Secukinumab group**: Subjects (or trained caregivers) will self-administer (or administer to the subject) a dose of secukinumab 300 mg s.c. (two injections of the 150 mg prefilled

[redacted]

syringes) once weekly for five weeks (at Randomization, 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 during the Double-blind Induction Period, placebo s.c. doses (two injections of the placebo to 150 mg prefilled syringe) will be self-administered by the subjects (or trained caregivers) at Weeks 13, 14 and 15.

2. **Placebo group**: Subjects (or trained caregivers) will self-administer (or administer to the subject) a dose of placebo s.c. (two injections of the placebo prefilled syringes) once weekly for five weeks (at Randomization, Weeks 1, 2, 3, and 4), followed by a dose after four weeks at Week 8.

   Beginning at Week 12, all subjects in the placebo group will be switched to treatment with secukinumab 300 mg s.c. Subjects will receive a dose of secukinumab 300 mg s.c. 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.

All subjects who enter the Double-blind Induction Period will self-administer the Week 12 dose following the completion of all assessments scheduled to be performed at Visit 8/Week 12 (Table 6-1).

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

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 Rand, Wks 1, 2, 3, 4 and 8	2x s.c. secukinumab 150 mg injection at Wk 12	2x s.c. secukinumab 150 mg injection at Wks 16 - 48
		2x s.c. secukinumab 150 mg PBO injection at Wks 13, 14 and 15	
Placebo (PBO)			
	2x s.c. secukinumab 150 mg PBO injection at Rand, 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 Wks 16 – 48

DB = Double-blind; OL = Open-label; Rand = Randomization; Wk = Week

5.3 Treatment Assignment, randomization

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

[redacted]

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and Investigators/site staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the two 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 (DSM) using a validated system that automates the random assignment of medication numbers to boxes containing the study treatments(s).

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

5.4 Treatment blinding

Subjects, 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 52, 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 subjects 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 subject-level data will remain blinded until the end of the trial.

Unblinding will only occur in the case of subject emergencies (see Section 5.5.12), 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 52 will be performed when all subjects have completed the Week 52 visit.

[redacted]

5.5 Treating the subject

5.5.1 Subject numbering

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

Upon signing the informed consent form, the subject 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 subject to register them into the IRT. The site should select the eCRF book with a matching Subject Number from the EDC system to enter data.

If a subject fails to be randomized for any reason, the IRT must be notified that the subject was not randomized. The reason for not being randomized will be entered on the Screening Phase Disposition eCRF.

5.5.2 Dispensing the study treatment

Each study site will be supplied by Novartis with secukinumab and placebo treatment in packaging of identical appearance. The secukinumab and placebo treatment packaging has a 2-part label. A unique medication number is printed on each part of this label.

Investigator/qualified site staff will identify the study treatment box(es) to dispense to the subject by contacting the IRT and obtaining the unique medication number(s). Immediately before dispensing the study treatment to the subject, site staff will detach the outer part of the label from the box and affix it to the Drug Label Form source document for that subject.

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

5.5.3 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated site staff have access. Upon receipt, all study treatment should 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 via the Clinical Trial Drug Supply Complaint Review Form, 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.

[redacted]

Study treatment should not 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 subject except for the medication number.

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

5.5.3.1 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Throughout the duration of the study, all doses of study treatment (secukinumab 300 mg and placebo) will be self-administered subcutaneously (s.c.) by the subject (or trained caregiver) after all study assessments for each visit have been completed. The prefilled syringes will be provided by the site staff to the subject, 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 subject.

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. Instructions on the self-administration of the study treatment and disposal of used prefilled syringes are detailed in the secukinumab Instructions For Use (IFU) document and will be provided to each subject.

At the beginning of the study, the Investigator/qualified site staff will determine if self-administration is appropriate for the subject, e.g., manual dexterity, ability to follow the IFU. If a subject requires a caregiver to administer study treatment, the caregiver will be trained by the Investigator/qualified site staff. If a caregiver is not available at a particular visit or the subject is having problems with self-administration, the Investigator/qualified site staff may administer the study treatment to the subject.

[redacted]

A different body site should be chosen each time a dose is administered. 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 far as possible, the injection site should be changed from administration to administration throughout the study. Subjects should self-administer the study treatment to one of the following body regions, changing the injection site routinely: the front of the thighs, the lower stomach area (abdomen) but **not** the area two inches around the navel. In cases where a caregiver will administer the study treatment, the upper outer arms may also be used as an injection site.

The first study treatment self-administration will occur at Visit 2/Baseline after inclusion/exclusion criteria have been confirmed, all scheduled study assessments have been performed, and the clinical report from the Visit 2/Baseline FDG-PET/CT scan has been received and reviewed with no clinically important findings that would preclude the subject from continuing in the study. The first dose of study treatment will take place under the supervision of the Investigator/qualified site staff. The subject will be instructed on the use of the secukinumab/placebo prefilled syringe via review of the secukinumab IFU. At subsequent visits, the Investigator/qualified site staff will observe the self-administration of secukinumab/placebo at the site.

Administration

Each dose of study treatment (two prefilled syringes of secukinumab 150 mg or placebo) will be packed in an individual box. For further details about study treatment storage and handling, please refer to the secukinumab IFU distributed as training material for the study.

During the Double-blind Treatment Period (from Randomization through Week 8), subjects will self-inject a total of 12 secukinumab or placebo injections (two injections per visit).

During the Double-blind Induction Period (from Week 12 through Week 15), subjects will self-inject a total of 8 injections (two injections at Week 12, and two injections at home at Weeks 13, 14 and 15).

During the Open-label Treatment Period (from Week 16 through Week 52), subjects will self-inject a total of 18 injections (two injections per visit at Weeks 16, 24, 32, 40, and 48 and two injections at home at Weeks 20, 28, 36, and 44).

Date and time of secukinumab or placebo self-administrations during the study must be recorded on the Dosage Administration Record eCRF.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and/or interruptions are not permitted.

5.5.6 Rescue medication

Rescue medication is not permitted in this study.

[redacted]

5.5.7 Concomitant treatment

All treatments administered during the six months prior to the Randomization visit (including any treatments started during the screening period) for any reason NOT including psoriasis will be entered on the Prior and Concomitant Medications eCRF or the Surgical and Medical Procedures eCRF with the reason for administration.

Psoriasis treatments used from the time the subject started to treat his/her psoriasis will be reported on the Prior Psoriasis Therapy eCRF. All topical treatments, systemic treatments, and phototherapies for psoriasis administered prior to randomization will be recorded (Section 6.2.2).

The Investigator should instruct the subject to notify site staff about any new treatments he/she takes after the start of the study treatment. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject starts study treatment must be recorded on the Prior and Concomitant Medications eCRF or the Surgical and Medical Procedures eCRF as appropriate. Information recorded will include indication for use, dosage, and dates of administration.

5.5.8 Prohibited Treatment

Use of any treatments displayed in Table 5-2 that could confound the efficacy of the study drug are **not** allowed during the study for any indication; wash-out periods for these treatments are provided in Table 5-2. If the use of these treatments is required, then the subject must **not** be randomized into the study.

The Investigator/qualified site staff must instruct the subject to notify them about any new treatments he/she takes after the start of the study treatment. All prohibited medications and significant non-drug therapies administered after the subject starts study treatment must be listed on the Prior and Concomitant Medications eCRF and the Surgical and Medical Procedures eCRF as appropriate, or the Concomitant Medications-Topical Corticosteroids eCRF for any TCS used after randomization.

If a prohibited treatment listed in Table 5-2 was used during the study, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study. If, in the Investigator's clinical judgment, the subject's use of a prohibited treatment presents an undue safety risk for the subject, the subject **must** be discontinued from study treatment as per Section 5.5.9.

If a subject receives a live virus vaccination during the study, the subject **must** discontinue study treatment and complete an end-of-treatment visit (either Visit 8/Week 12 EOT1 or Visit 14/Week 52 EOT2).

Any other protocol deviation that results in a significant risk to the subject's safety will be recorded.

[redacted]

Exposure to light

Subjects will be advised to limit exposure to ultraviolet (UV) light (including sunbathing and/or use of UV tanning devices) during the study to avoid possible effects on psoriasis.

Table 5-2 Prohibited treatment

Prior Therapy (Before Visit 2/Baseline)	
Prohibited Treatments[†,‡]	**Washout Period (before Randomization)**
Secukinumab	No prior use allowed
Any biologic drug directly targeting IL-17 or the IL-17 receptor (other than secukinumab)	No prior use allowed
Alefacept, briakinumab, efalizumab, ustekinumab	6 months
Biological immunomodulating agents other than above (e.g., adalimumab, infliximab, etanercept)	3 months
Cholesterol-lowering medication (e.g., statins)	Dose must be stable for ≥90 days prior to randomization and remain stable for the duration of the study
Other systemic immunomodulating treatments[§] [e.g., MTX, cyclosporine A, corticosteroids (oral, i.v., intramuscular, s.c., intra-articular, transdermal)[§], 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
Any 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

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, and 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

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

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

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

5.5.9 Discontinuation of study treatment

Subjects may voluntarily discontinue study treatment for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. Subjects who prematurely withdraw from the study will not be replaced.

If discontinuation occurs for any reason during the study, the Investigator/qualified site staff must make every effort to determine the primary reason for a subject's discontinuation from the study. This information will then be recorded on the End of Treatment eCRF for either the Double-blind Treatment Period (Visit 8/Week 12 EOT1), or the Double-blind Induction and Open-label Treatment Periods (Visit 14/Week 52 EOT2) as appropriate.

Study treatment must be discontinued and the subject withdrawn from the study if the Investigator on balance believes that continuation would be detrimental to the subject's well-being. Study treatment **must** be discontinued under the following circumstances:

- Emergence of the following AEs: AEs that in the judgment of the Investigator/qualified site staff, taking into account the subject's overall status, prevent the subject from continuing study treatment (for example, sepsis or serious infection);
- Any laboratory abnormalities that in the judgment of the Investigator/qualified site staff, taking into consideration the subject's overall status, prevents the subject from continuing study treatment;
- Pregnancy (see Section 6.5.6 and Section 7.3);
- Ongoing use of any prohibited treatment, use of a prohibited treatment that results in an undue safety risk for the subject as per the Investigator's clinical judgment, or receipt of a live virus vaccine during the study (as detailed in Section 5.5.8);
- Emergency unblinding;
- Any other protocol deviation that results in a significant risk to the subject's safety or significantly affects the validity of the study assessments.

Subjects who discontinue study treatment should undergo an end of study visit and then be discontinued from the trial.

- **Double-blind Treatment Period:** For subjects who discontinue study treatment prematurely before the end of the Double-blind Treatment Period, the Visit 8/Week 12 EOT1 assessments should be performed. **NOTE: Consultation with the Medical Monitor is required to**

[redacted]

determine if the FDG-PET/CT scan assessment should be performed during the discontinuation visit.

- **Double-blind Induction and Open-label Treatment Periods:** For subjects who discontinue study treatment prematurely before the end of the Double-blind Induction or Open-label Treatment Periods, Visit 14/Week 52 EOT2 visit should be performed. **NOTE**: **Consultation with the Medical Monitor is required to determine if the FDG-PET/CT scan assessment should be performed during the discontinuation visit.**

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

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

Scheduling of the end of treatment discontinuation visit

At the time of the end of study discontinuation visit, IF it has been approximately 4 weeks post last dose of study treatment, THEN the assessments for Visit 8/Week 12 EOT1 (for early discontinuation during **the Double-blind Treatment Period**) or for Visit 14/Week 52 EOT2 (for early discontinuation during **Double-blind Induction** or **Open-label Treatment Periods**) should be completed.

IF it has not been approximately 4 weeks post last dose of study treatment at the time of the end of study discontinuation visit, THEN the subject should be scheduled to return 4 weeks post last dose for their Visit 8/Week 12 (for early discontinuation during the **Double-blind Treatment Period**) or Visit 14/Week 52 (for early discontinuation during the **Double-blind Induction** or **Open-label Treatment Periods)** assessments.

The Investigator/site staff must also contact the IRT to register the subject's discontinuation from the study.

5.5.10 Withdrawal of consent

Subjects may voluntarily withdrawal consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject does not want to participate in the study anymore, and does not want any further visits or assessments, and does not want any further study-related contacts, and does not allow analysis of already-obtained biologic material.

If a subject withdraws consent, the Investigator must make every effort (e.g., telephone, email, letter) to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communication or follow-up.

[redacted]

5.5.11 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the Investigator should show "due diligence" by contacting the subject, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc.

5.5.12 Emergency breaking of assigned treatment code

Emergency breaking of the assigned treatment code should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition.

Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The Investigator will then receive details of the study treatment for the specified subject and a fax or email confirming this information. The system will automatically inform Novartis and CRO study personnel that the code has been broken.

It is the Investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency.

Study treatment must be discontinued in the event of an emergency unblinding.

5.5.13 Study completion and post-study treatment

A subject's individual study participation is completed once Visit 14/Week 52 of Open-label Treatment has been completed. After this date, any SAEs that occur in the following 30 days must be reported. The Investigator will also follow any AEs for which there is no outcome that can be reported at the final study visit.

The study as a whole will be completed once all randomized subjects have completed the study as per the protocol and the clinical database has been locked. Recruitment into the study will be terminated by the sponsor once the targeted number of randomized subjects has been met or is foreseen to be met with the subjects already in screening. Subjects who have been screened and have a screening visit recorded in the IRT system at the time that the planned enrollment number is met will be allowed to enter the trial and to be randomized if they are eligible.

Upon completion of their study participation, subjects will return to individual treatment, as determined by their treating physician.

The Investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

[redacted]

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the subject should be seen as soon as possible and treated as a prematurely withdrawn subject (as described in Section 5.5.9). The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The Investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "X" when the assessments are to be performed.

Subjects should be seen for all visits on the designated day or as close as possible to the original planned visit schedule (recommended visit windows are in Table 6-1. Every effort should be made to respect the time frame for the Visit 8/Week 12 visit.

At a minimum, subjects will be contacted for safety evaluations during the 30 days following the last study visit, including a final contact at the 30-day point. Documentation of attempts to contact the subject should be recorded in the source documentation.

Visit windows

A "visit window" will be allowed during the study as follows:

- Screening Period
  - +2 days (for a total of up to 30 days)
- Double-blind Treatment Period
  - ± 2 days for Visits 3-8
- Open-label Treatment Period
  - ± 7 days for Visits 9-14

Rescreening

Rescreening may be allowed under certain conditions. Requests from the Investigator/site staff to rescreen subjects 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 subject was previously randomized into the study.

If a subject rescreens for the study, the subject must sign a new ICF and be issued a new subject number. The date of the new informed consent signature should correspond to the new subject number. Informed consent for a rescreened subject must be obtained prior to performing study-related assessments or collecting any data for the Screening Visit. For rescreening, all

[redacted]

screening assessments must be performed as per protocol, except for the tuberculosis (TB) work up, if applicable, if performed not more than 12 weeks before randomization.

If the date of a 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 subject must repeat the QuantiFERON test performed by the central laboratory.

Unscheduled visits

Subjects may be seen at any time for an unscheduled visit, e.g., if they experience deterioration of psoriasis or AEs that in the opinion of the Investigator/qualified site staff need intervention or repeat laboratory testing. The assessment(s) performed at an unscheduled visit must include at minimum: an assessment of concomitant medication and procedures/significant non-drug therapies, vital signs, and an AE/SAE assessment. Any additional assessments performed are at the Investigator/qualified site staff's discretion. 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										Unscheduled Visit [D]
Visit	1	2	3	4	5	6	7	8 / EOT1 [A,B]				9		10		11		12		13	14 / EOT2 [C]	
Week	-4 to BL [E]	BL	1	2	3	4	8	12	13	14	15	16	20	24	28	32	36	40	44	48	52	
Visit window (Days)			±2	±2	±2	±2	±2	±2				±7		±7		±7		±7		±7	±7	
Assessment																						
Obtain informed consent	X																					
Demographics	X																					
Inclusion/exclusion criteria [F]	X	X																				
Smoking and alcohol history	X																					
Psoriasis history / Prior psoriasis therapy / Psoriatic arthritis history	X																					
Cardiovascular medical history	X																					
Cardiovascular disease family history	X																					
Medical history / Current medical conditions	X																					
Prior and concomitant medications / Surgical and medical procedures	X	X	X	X	X	X	X	X				X		X		X		X		X	X	X
Physical examination [F]	X	X						X						X							X	X [d]
Height	X																					

[redacted]

Period	**SCR**	**Double-blind Treatment Period**							**Double-blind Induction Period**			**Open-label Treatment Period**										**Unscheduled Visit** [D]
Visit	1	2	3	4	5	6	7	8 / EOT1 [A,B]				9		10		11		12		13	14 / EOT2 [C]	
Week	-4 to BL[E]	BL	1	2	3	4	8	12	13	14	15	16	20	24	28	32	36	40	44	48	52	
Visit window (Days)			±2	±2	±2	±2	±2	±2				±7		±7		±7		±7		±7	±7	
Assessment																						
Weight	X	X				X	X	X				X		X		X		X		X	X	X[d]
Vital signs	X	X				X	X	X				X		X		X		X		X	X	X
Lab analysis: Safety panel (chemistry, hematology)[G]	X							X						X							X	X[d]
Fasting labs: plasma glucose	X																					
Viral serology lab analysis: HIV, Hepatitis B and C [G]	X																					X[d]
QuantiFERON® TB-Gold In-Tube test [G,H]	X																					X[d]
Serum pregnancy test [G,I]	X																					X[d]
Urine pregnancy test (local)[J]		X						X													X	X[d]
FDG-PET CT[K]		X[L]						X[M]													X	
Blood sample for cardio-metabolic biomarkers[G]		X*				X	X	X*						X				X			X*	
PASI	X	X				X	X	X				X		X		X		X		X	X	X[d]
IGA mod 2011	X	X				X	X	X				X		X		X		X		X	X	X[d]
Alcohol use assessment			X	X	X	X	X	X				X		X		X		X		X	X	X[d]
DLQI		X						X						X		X		X		X	X	

[redacted]

Period	**SCR**	**Double-blind Treatment Period**							**Double-blind Induction Period**			**Open-label Treatment Period**										**Unscheduled Visit** [D]
Visit	1	2	3	4	5	6	7	8 / EOT1 [A,B]				9		10		11		12		13	14 / EOT2 [C]	
Week	-4 to BL[E]	BL	1	2	3	4	8	12	13	14	15	16	20	24	28	32	36	40	44	48	52	
Visit window (Days)			±2	±2	±2	±2	±2	±2				±7		±7		±7		±7		±7	±7	
Assessment																						
AE/SAE assessment [N]	X	X	X	X	X	X	X	X				X		X		X		X		X	X	X
Randomization via IRT		X																				
Subject self-administration of study treatment at site		X	X	X	X	X	X	X				X		X		X		X		X		
Dispense study treatment to subject for at-home dosing								X				X		X		X		X				
Subject self-administration of study treatment at home and completion of Self-Administration Log[O]									X	X	X		X		X		X		X			
At-home Dosing Phone Reminder[F,P]										X			X		X		X		X			
Check Self-Administration Log and returned used/unused study treatment and packaging[F,Q]												X		X		X		X		X		X[d]

AE=adverse event; BL = Baseline; DLQI=Dermatology Life Quality Index; EOT1=End of Treatment 1; EOT2=End of Treatment 2; FDG-PET CT=18-fluorodeoxyglucose positron emission tomography with computer assisted tomography; HIV=human immunodeficiency virus; IGA=Investigator's Global Assessment; IRT=Interactive Response Technology; PASI=Psoriasis Area and Severity Index; SAE=Serious Adverse Event; SCR=Screening; TB=tuberculosis

* At Visits 2, 8, and 14, subjects are required to be fasting for a minimum of 8 hours prior to the blood sample collection for cardiometabolic biomarkers

[redacted]

Period	SCR	Double-blind Treatment Period							Double-blind Induction Period			Open-label Treatment Period										Unscheduled Visit [D]
Visit	1	2	3	4	5	6	7	8 / EOT1 [A,B]				9		10		11		12		13	14 / EOT2 [C]	
Week	-4 to BL[E]	BL	1	2	3	4	8	12	13	14	15	16	20	24	28	32	36	40	44	48	52	
Visit window (Days)			±2	±2	±2	±2	±2	±2				±7		±7		±7		±7		±7	±7	
Assessment																						

[A] Subjects will complete all Visit 8/Week 12 assessments prior to administration of study treatment

[B] Visit 8/Week 12 assessments must be performed for subjects who discontinue treatment during the Double-blind Treatment Period. Consultation with the Medical Monitor is required to determine if the FDG-PET/CT scan assessment should be performed during the discontinuation visit.

[C] Visit 14/Week 52 assessments must be performed for subjects who discontinue treatment prematurely during the Double-blind Induction or the Open-label Treatment Periods. Consultation with the Medical Monitor is required to determine if the FDG-PET/CT scan assessment should be performed during the discontinuation visit.

[D] Unscheduled visit – concomitant medications, vital signs, and AE/SAE assessment are required for an unscheduled visit; all other assessments are performed at the discretion of the Investigator

[E] Visits 1 and 2 must not be performed on the same day

[F] These assessments are supported by and stored within the source documentation. Data relating to inclusion/exclusion criteria are captured in the corresponding eCRF.

[G] Samples will be shipped to a central laboratory for analysis

[H] A repeat QuantiFERON® TB-Gold In-Tube test is recommended if the result of the first QuantiFERON® TB-Gold In-Tube test is “indeterminate”. The subject must be referred for a follow-up tuberculosis workup (as per local guidelines) if either the first or the repeat test is “positive” or if the results of both tests are “indeterminate”. If the first test is indeterminate, the Investigator may decide not to repeat the test and to proceed directly to the workup, though this is not recommended. 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.

[I] A serum pregnancy test is not required for a woman who is sterile or who is post-menopausal.

[J] A urine pregnancy test is not required for a woman who is sterile or who is post-menopausal. In the event of a positive urine pregnancy test, study treatment must be withheld and a serum pregnancy test performed at the same visit.

[K] The FDG-PET/CT scan will be performed at each site’s local imaging center. A clinical reading scan report will be provided to the site within 24 hours of the scan by the local imaging center.

[redacted]

Period	SCR	Double-blind Treatment Period							Double-blind Induction Period			Open-label Treatment Period										Unscheduled Visit [D]
Visit	1	2	3	4	5	6	7	8 / EOT1 [A,B]				9		10		11		12		13	14 / EOT2 [C]	
Week	-4 to BL[E]	BL	1	2	3	4	8	12	13	14	15	16	20	24	28	32	36	40	44	48	52	
Visit window (Days)			±2	±2	±2	±2	±2	±2				±7		±7		±7		±7		±7	±7	
Assessment																						

[L] The Visit 2/Baseline FDG-PET/CT scan report must have been reviewed with no clinically significant findings prior to randomization and administration of the initial dose of study treatment (see Section 3.1.1.1 for additional information). Randomization must occur 7 days or less from date of FDG-PET/CT scan.

[M] The Visit 8/Week 12 FDG-PET/CT must have been reviewed with no clinically significant findings prior to the administration of the Visit 8/Week 12 dose (see Section 3.1.2.1 for additional information). Subjects must administer their Week 12 dose 7 days or less from the date of their Week 12 FDG-PET/CT scan.

[N] AE/SAE assessment includes injection site reactions

[O] Subjects will self-administer study treatment at home at these time points and will record each dose administered at home in their Self-Administration Dosing Log

[P] Site staff to contact subject via telephone to assess subject compliance with at-home dosing and completion of Self-Administration Log

[Q] The at-home administrations of study treatment will be recorded by the subject on the Self-Administration Log which must be returned to the site at the next visit along with the used/unused study treatment and the outer boxes for a compliance check.

[redacted]

6.1 Information to be collected on screening failures

All subjects who sign informed consent but discontinue prior to randomization at Visit 2 are considered screening failures.

If a subject discontinues prior to randomization at Visit 2, the IRT must be notified about the discontinuation, and the primary reason for the screen failure should be entered in the Screening Phase Disposition eCRF.

The Screening Visit Date, Demography, Informed Consent, Inclusion/Exclusion Criteria, Subject Rescreening, and the Screening Phase Disposition eCRFs must be completed. The Adverse Event eCRF and a paper SAE form must be completed for any serious adverse event (SAE) that occurs 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 Informed Consent eCRF must be completed if consent was withdrawn during the Screening period before the subject was randomized.

6.2 Subject demographics/other baseline characteristics

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

6.2.1 Demographics

Subject demographic data to be collected on all subjects include: date of birth, subject initials, sex, race, ethnicity and child-bearing potential (for females only).

6.2.2 Psoriasis history / Prior psoriasis therapies

Disease history will be collected at the screening visit. The information to be collected and entered in the eCRF includes the following:

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

6.2.3 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.

[redacted]

6.2.4 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.

6.2.5 Comorbidities – cardiovascular history

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

Additionally, family history of certain cardiovascular diseases will also be collected.

6.2.6 Relevant medical history / Current medical conditions

Relevant medical history/current medical conditions, not including psoriasis or psoriatic arthritis, will be recorded on the Medical History eCRF.

Relevant medical history/current medical conditions will include data up to six months prior to signing of the informed consent. Whenever possible, diagnoses (and not symptoms) will be recorded.

Significant findings that are observed after the subject has provided informed consent, and that meet the definition of an AE, must be recorded on the Adverse Event 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.

6.2.7 Prior and concomitant medications

Concomitant medications and prior medications taken over the six months preceding study enrollment will be captured at the Screening visit, and updated at Visit 2/Baseline.

6.2.8 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 subject's TB status.

[redacted]

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 subjects. This test will only be used to determine subject's eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection (Doherty, Van Vorhees and Lebwohl l 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 subject is not exposed to the vaccine. The assay measures the production of interferon-gamma and presents it relative to a negative and a positive control sample (Manuel and Kumar 2008).

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

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

- If the test result is **negative**, the subject may be randomized
- If the test result is **positive**, the Investigator should perform a TB workup for the test result as per local procedures.
  - Subjects **positive** for latent TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration.
  - Subjects **positive** for active TB per workup are not eligible for the study.
  - Subjects **negative** for TB (no signs of latent or active TB) per workup may be randomized to the trial.
- 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 subject may be randomized.
  - If the second test is positive or indeterminate, the Investigator should perform a TB workup as per local guidelines. 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.

Refer to Section 13 (Appendix 2) to see a schematic of the tuberculosis screening process and subject eligibility with respect to TB testing.

[redacted]

6.2.9 Other baseline characteristics

Baseline characteristic data to be collected on all subjects include (all labs are central except where indicated) (see also Table 6-1):

- vital signs, hematology, clinical chemistry, viral serology (HIV, Hepatitis B and Hepatitis C), serum pregnancy, physical examination, height, weight; PASI, IGA mod 2011; DLQI.

6.3 Treatment exposure and compliance

All administered doses of secukinumab or placebo will be recorded on the Dosage Administration Record eCRF. Compliance will be assessed by Novartis and CRO study personnel using the Dosage Administration Record eCRF, medication numbers, Drug Label Form information, and information collected by IRT.

Subjects 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. Subjects will be instructed to return to the study site at 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. Subjects 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. At the final study visit (Visit 14/Week 52), the subject's Self-Administration Log will be retained in the subject's source documents.

The Investigator/qualified site staff should promote compliance by instructing subjects to attend the study visits as scheduled, to take the study treatments exactly as prescribed, and by reiterating that compliance is necessary for subject safety and the validity of the study. Additionally, sites will be instructed to contact subjects via telephone at the time of scheduled at-home dosing to check compliance and to ensure completion of the Self-Administration Log. Likewise, subjects 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.

6.4 Efficacy

The primary efficacy variable is the change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio from the aorta. The primary analysis time point will be at Week 12.

The secondary efficacy variables are the following:

- Change from baseline in cardiometabolic biomarkers (cardiometabolic function [lipid particle size, HDL function (cholesterol efflux)], measures of inflammation [TNF-Alpha, IL-6, C-reactive protein, GlycA], adiposity [leptin and adiponectin], insulin resistance [insulin

[redacted]

levels/glucose to yield HOMA-IR], and markers predictive of diabetes [apolipoprotein B, ferritin, IL-2 receptor A, IL-18, and fetuin-A])

- PASI 75 response (yes, no)
- PASI 90 response (yes, no)
- PASI 100 response (yes, no)
- IGA mod 2011 score of 0 or 1 (yes, no)
- Change from baseline in DLQI total score

All efficacy assessments should be performed prior to the administration of study treatment and at all scheduled study visits as indicated in Table 6-1.

Patient Reported Outcomes (PRO)

PROs should be collected prior to the Investigator performing any efficacy assessments:

- DLQI

Efficacy assessments (Investigator)

The following efficacy assessments performed by the Investigator will be completed for all subjects:

- PASI
- IGA mod 2011

6.4.1 Target (arterial vascular uptake) to background (venous blood pool) ratio from the aorta

Subjects will undergo vascular inflammation imaging assessments with full-body FDG-PET/CT scans at three scheduled visits – Visit 2/Baseline, Visit 8/Week 12 and Visit 14/Week 52 (see Table 6-1). The FDG-PET/CT scans will be conducted at each investigative site's local imaging center and the whole process should take approximately 3 hours to complete.

Subjects will be required to fast for a minimum of 8 hours prior to the imaging assessment. At the imaging center, the subject's glucose level will be checked by finger stick test and results should not exceed 150 mg/dL. If the glucose level exceeds 150 mg/dL, consultation with the Medical Monitor prior to the imaging will be required to determine if the subject is eligible to continue in the study. The whole-body PET/CT scan will be initiated approximately 120 minutes (± 10 minutes) after intravenous administration of [18F]-fluorodeoxyglucose (FDG).

Within approximately 24 hours after the completion of the FDG-PET/CT scan, the local nuclear medicine personnel will issue a clinical report determining if the subject has any clinically significant findings which would preclude the subject's continued participation in the study.

The arterial uptake of FDG will be measured by the standardized uptake value (SUV) max divided by the venous SUV mean (Mehta et al 2012). This will yield a target to background ratio

[redacted]

(TBR) which is considered the standard reporting variable in FDG-PET/CT vascular studies. The PET/CT images obtained from each site's local imaging center will be de-identified and should be sent to the [redacted] Imaging Lab within 1-3 days where trained nuclear medicine personnel will undertake a qualitative review of the PET/CT images. During this review, two-dimensional (2D) circular regions of interests (ROIs) will be manually placed on the PET images around the external aortic contour, around the hepatic margin, and around articular spaces on all transverse slices passing through these structures using low-dose CT images for anatomic guidance. The images will then be sent to the central core [redacted] Imaging Lab for measuring the SUVs. The [redacted] central PET/CT readers will be blinded to time and treatment via Digital Imaging and Communication in Medicine (DICOM) file editing applied by the [redacted].

The mean aortic SUV will be calculated for five segments of the aorta: ascending aorta, aortic arch, descending thoracic aorta, suprarenal abdominal aorta, and infrarenal abdominal aorta. These segments are defined to consider separately various regions of aortic disease that are associated with different clinical phenotypes (e.g., aortic arch disease with stroke, abdominal aortic disease with abdominal aortic aneurysm).

6.4.2 Cardiometabolic biomarkers

The following cardiometabolic biomarkers will be analyzed centrally at an analytical laboratory:

- Cardiometabolic function: lipid particle size, HDL function (cholesterol efflux);
- Inflammation: TNF-Alpha, IL-6, C-reactive protein, GlycA;
- Adiposity: leptin and adiponectin;
- Insulin resistance: insulin levels/glucose to yield HOMA-IR;
- Markers predictive of diabetes: apolipoprotein B, ferritin, IL-2 receptor A, IL-18, and fetuin-A.

Blood samples for cardiometabolic biomarkers will be collected at the scheduled time points as indicated in Table 6-1.

Subjects will be required to fast for a minimum of 8 hours prior to the blood draw for the cardiometabolic biomarkers at the following visits only:

- Visit 2/Baseline
- Visit 8/Week 12
- Visit 14/Week 52.

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

[redacted]

6.4.3 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 subject. The Investigator is only responsible for collecting the components or scoring signs and total regional area. PASI calculations, including changes over time, will be done electronically, not by the Investigator.

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 6-3. 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 6-2.

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 is provided in Section 13 (Appendix 3).

[redacted]

Table 6-2 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%
	4=very severe	4=very severe	4=very severe	4=50-<70%
				5=70-<90%
				6=90-100%
Trunk (T)‡	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%
	4=very severe	4=very severe	4=very severe	4=50-<70%
				5=70-<90%
				6=90-100%
Upper limbs (U)	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%
	4=very severe	4=very severe	4=very severe	4=50-<70%
				5=70-<90%
				6=90-100%
Lower limbs (L)§	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%
	4=very severe	4=very severe	4=very severe	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 75 response**: subjects achieving ≥75% improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders
- **PASI 90 response**: subjects achieving ≥90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders
- **PASI 100 response/remission**: complete clearing of psoriasis (PASI=0)

6.4.4 Investigator's Global Assessment (IGA mod 2011)

The IGA mod 2011 will be conducted for overall psoriatic disease as indicated in Table 6-1. It is recommended that the same evaluator conducts the assessment throughout the study wherever possible.

Subjects require an IGA mod 2011 score at Randomization of 3 or 4 in order to participate in the study. Based on this scale, a subject will be considered as an IGA 0 or 1 responder if they achieve a score of 0 or 1, and improve by at least 2 points on the IGA scale at a given time point compared to their score at Randomization (Baseline).

The IGA mod 2011 rating scale for overall psoriatic disease is shown in Table 6-3.

The IGA mod 2011 used in this study is static, i.e. it refers exclusively to the subject's disease state at the time of the assessments, and does not attempt a comparison with any of the subject's previous disease states, whether at baseline or at a previous visit.

The IGA mod 2011 score will be recorded in the eCRF.

Table 6-3 IGA mod 2011 rating scale

Score	Short description	Detailed description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present
1	Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling
2	Mild disease	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling
3	Moderate disease	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling
4	Severe disease	Bright to deep dark red coloration; severe thickening with hard edges; severe / coarse scaling covering almost all or all lesions

NOTE: Involvement of the nails is not part of the assessment.

[redacted]

6.4.5 Health-related quality of life (HRQoL)

The impact of psoriasis on various aspects of the subject's health-related quality of life (HRQoL) will be assessed by the following validated instrument which will be performed at the scheduled study visits as indicated in Table 6-1:

- Dermatology Life Quality Index (DLQI)

The quality of life assessment should be completed by the subject prior to being seen by the study physician (Investigator or qualified site staff) who will perform the Investigator assessments.

The subject should be given sufficient space and time to complete the paper questionnaire. The study coordinator should check the questionnaire for completeness and encourage the subject to complete any missing responses.

Before the subject's clinical examination, the Investigator should review the completed questionnaire for responses that may indicate potential AEs or SAEs. If AEs or SAEs are confirmed, the Investigator must record the events as per instructions given in Section 7 of the protocol.

Investigators should not encourage subjects to change the responses reported in the completed questionnaire.

A copy of the DLQI is provided in Section 13 (Appendix 5).

6.4.5.1 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item general dermatology disability index designed to assess health-related quality of life in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral warts (Finlay and Khan, 1994). The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used; it has been tested across 32 different skin conditions and is available in 55 languages. The recall period is the last week, and the instrument requires 1 to 2 minutes for completion.

Each item has four response categories, ranging from 0 (not at all) to 3 (very much). "Not relevant" is also a valid response and is scored as 0. The DLQI total score is a sum of the 10 questions. Scores range from 0 to 30 and higher scores indicate greater health-related quality-of-life impairment. Additionally, each subscale of the DLQI may be analyzed separately.

The DLQI questionnaire (date of publication 1994) will be completed by the subject as indicated in Table 6-1.

6.4.6 Appropriateness of efficacy assessments

The primary efficacy assessment is aortic vascular inflammation measured by FDG-PET/CT, an important imaging biomarker and surrogate marker for future vascular risk. FDG-PET/CT is

[redacted]

reliable and predictive of future vascular events independent of other cardiovascular biomarkers, and improves rapidly (i.e., within four weeks) with interventions known to reduce vascular risk (i.e., statins). It is increasingly used as a surrogate marker for novel agents being studied in FDA regulated trials assessing novel strategies for CV risk reduction. Alternative assessments such as carotid IMT and MRI-based measures of wall thickness change only slowly and thus would require longer term trials in which use of placebo would not be feasible. Secondary efficacy assessments include biomarkers that are well established markers of inflammation and cardiovascular risk.

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

The IGA mod 2011 scale has been developed by Novartis in collaboration with health authorities, in particular the FDA. It is based on the previous version of the scale which was used in the Phase II secukinumab studies. In the modified scale, the two "very severe" and "severe" categories have been condensed into a single category of "severe", and the explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points.

6.5 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.

Safety assessments will be performed as indicated in Table 6-1:

- Evaluation of all AEs and SAEs (including injection site reactions and occurrence of infections)
- Physical examination
- Vital signs
- Height and weight
- Laboratory evaluations
  - Hematology
  - Clinical chemistry
  - Viral serology
- Pregnancy and assessments of fertility.

6.5.1 Physical examination

A complete physical examination will be performed by a professionally trained physician or health professional licensed to perform physical examinations, and listed on FDA Form 1572. The physical examination, including general appearance, will be performed at the scheduled study visits as indicated in Table 6-1.

[redacted]

If indicated, based on medical history and/or symptoms, additional exams may be performed at the discretion of the Investigator/qualified site staff.

If possible, assessments for an individual subject should be performed by the same Investigator/qualified 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 subject 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 must be recorded in the subject's Adverse Event eCRF (Section 7).

6.5.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed at scheduled study visits as indicated in Table 6-1.

After the subject has been sitting for at least five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure (BP) will be measured using a validated device with an appropriately sized cuff. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. The BP measurement will be recorded in the Vital Signs eCRF.

If possible, assessments should be performed by the same site staff throughout the study.

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 subject. No specific action is foreseen as part of the study protocol.

6.5.3 Height and weight

Height and body weight (in indoor clothing but without shoes) will be measured at scheduled study visits as indicated in Table 6-1. If possible, body weight assessments should be performed using the same scale throughout the study.

[redacted]

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collection, shipment of samples, and reporting of results by the central laboratory will be provided to Investigators in the Laboratory Manual.

Refer to the Laboratory Manual for identification of laboratory reference range values, notable values, and the schema for notification of site staff and Novartis for out of range values.

Section 13 (Appendix 1) shows the expanded laboratory ranges and the clinically notable abnormalities of key laboratory tests.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count will be measured at scheduled study visits as indicated in Table 6-1.

6.5.4.2 Clinical chemistry

Blood urea, creatinine, total bilirubin, ALT (SGPT), AST (SGOT), GGT, alkaline phosphatase, and hemoglobin A1c (HbA1c) will be measured at scheduled study visits as indicated in Table 6-1; HbA1c will be measured at screening only.

6.5.4.3 Fasting laboratory evaluations

Fasting (8 hour duration with water *ad libitum*) laboratory tests will be performed at screening and will include:

- Plasma glucose

6.5.4.4 Viral serology

Viral serology will be performed at screening and will include:

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

To be eligible for randomization, subjects must have "non-reactive" serology results at screening.

6.5.5 Pregnancy and assessments of fertility

At the Screening visit, a serum β-hCG pregnancy test will be performed in all women except those who are sterile or post-menopausal. Any woman with a confirmed positive pregnancy test during screening is not eligible for randomization.

[redacted]

Starting at Visit 2/Baseline, all women except those who are sterile or post-menopausal will have a local urine pregnancy test at scheduled study visits as indicated in Table 6-1.

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 subject must be discontinued from the study as described in Section 5.5.9.

6.5.6 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.

6.6 Other assessments

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

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Study treatment includes the study drug under evaluation and the comparator treatment or placebo that is given during any phase of the study. Medical conditions/diseases present at the time of screening are only considered AEs if they worsen after the subject has signed informed consent.

For all subjects who sign informed consent and who are randomized into the Double-blind Treatment Period of the study will have all adverse events that occur **after informed consent is signed** recorded on the Adverse Event CRF.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, 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; and/or
- they require therapy.

[redacted]

Clinically significant abnormal laboratory values or test results should 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 subject with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

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

- 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
- Relationship to the study treatment
- Duration (start and end dates or if continuing at final exam)
- Whether it constitutes a serious adverse event (SAE - See Section 7.2 for the definition of SAE)
- Action taken regarding study treatment
- Concomitant medication(s) taken or non-drug therapies given
- Outcome.

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

Information about common side effects already known about the study drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications (INs). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

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

[redacted]

- 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 subject's general condition
- is medically significant, i.e. defined as an event that jeopardizes the subject 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 subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see 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 subject 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 (see Annex IV, ICH-E2D Guideline).

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

All AEs (serious and non-serious) are captured on the eCRF, SAEs also require individual reporting to DS&E as per Section 7.2.2.

7.2.2 SAE reporting

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

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted

[redacted]

within 24 hours of the Investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (*either initial or follow up information)* is collected and recorded on the paper Serious Adverse Event Report Form. The Investigator must assess the relationship to *each specific component of study treatment (if study treatment consists of several drugs)* complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

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 investigational 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 investigational 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 Pregnancy reporting

To ensure subject safety, each pregnancy occurring while the subject is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on the Clinical Trial Pregnancy Form and be reported by the Investigator/qualified site staff 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 must be reported on the SAE Report Form.

[redacted]

8 Data review and database management

8.1 Site monitoring

At a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of entries on the eCRFs, 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 investigator staff must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a CRO. Additionally, a CRO may analyze data and identify risks and trends for site operational parameters, and provide reports to the Novartis Clinical Team to assist with trial oversight.

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

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

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs) using fully validated software that conforms to US 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained.

Automatic validation programs check for data discrepancies 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 via electronic approval that the data entered into the eCRFs are complete and accurate. After database lock, the Investigator will receive copies of the subject data for archiving at the investigational site.

[redacted]

8.3 Database management and quality control

A CRO working on behalf of Novartis will review the data entered into the eCRFs 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.

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 (including cardiometabolic biomarkers) will be processed centrally and the results will be sent electronically to a designated CRO.

FDG-PET/CT scans will be read and analyzed centrally and the results will be sent electronically to a designated CRO.

A PRO questionnaire will be completed by the subject on paper, and the data transcribed into the eCRF by investigator site staff.

Randomization codes and data about all study drug(s) dispensed to the subject will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to 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 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.

[redacted]

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

Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

Efficacy, safety, and other data will be summarized. 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.

9.1 Analysis sets

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

Randomized Set: The randomized set includes all subjects who were randomized.

Safety Set: The Safety Set includes all subjects who received at least one dose of study medication. Subjects will be analyzed according to treatment received.

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

9.2 Subject demographics and other baseline characteristics

Data will be summarized with respect to demographic and baseline characteristics for the Randomized Set and the Full Analysis Set.

9.3 Treatments

The number of subjects and the length of time (in days) exposed to each treatment will be summarized for the Safety Set. Note that during the Double-blind Treatment Period, all subjects will receive their last dose of study treatment at Visit 7/Week 8.

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. Summaries for cardiovascular and psoriasis-specific medical history will be provided as well.

[redacted]

9.4 Analysis of the primary variable

9.4.1 Variable

The primary efficacy variable is the change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio from the aorta. Target to background ratio is considered the standard reporting variable based on FDG-PET/CT scans in vascular studies (see Section 6.4.1). The primary analysis time point will be at Week 12.

9.4.2 Statistical model, hypothesis, and method of analysis

Let μ_j denote the population mean of change from baseline in the target to background ratio from the aorta at Week 12 for treatment group j, j = 0, 1, where 0 corresponds to placebo and 1 corresponds to secukinumab.

The following null hypothesis (H_0) will be tested against the alternative hypothesis (H_A):

$$H_0: \mu_1 - \mu_0 = 0$$

$$H_A: \mu_1 - \mu_0 \neq 0$$

The primary efficacy variable will be analyzed by an analysis of covariance (ANCOVA) model with treatment, baseline, and body weight (<90 kg, ≥90 kg) as explanatory variables. The least squares means of the two treatment groups, least squares mean difference of the treatment groups, 95% confidence interval for the difference in the two treatment groups, and p-value based on the fitted linear model will be reported.

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

9.4.3 Handling of missing values/censoring/discontinuations

Missing data will be imputed using the last-observation-carried-forward (LOCF) method. If a subject has no post-baseline value, the missing value will not be imputed and the subject will be removed from the analysis.

9.4.4 Supportive analyses

A supportive nonparametric analysis will be performed to examine the consistency of results if the assumption of normality for the distribution of the primary efficacy variable is not tenable. For this supportive analysis, the primary efficacy variable will be analyzed using the stratified Wilcoxon rank-sum test with modified ridit scores (van Elteren's test), adjusting for body weight (<90 kg, ≥90 kg) (Stokes, Davis, and Koch, 2012).

[redacted]

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary efficacy variables are the following:

- Change from baseline in each biomarker (see Section 6.4)
- PASI 75 response (yes, no)
- PASI 90 response (yes, no)
- PASI 100 response (yes, no)
- IGA mod 2011 score of 0 or 1 (yes, no)
- Change from baseline in DLQI total score

Change from baseline in each biomarker and change from baseline in DLQI total score will be analyzed at each time point using the same ANCOVA model as for the primary efficacy variable, and missing data will be imputed using the LOCF method.

IGA mod 2011 score of 0 or 1 and PASI 75 / 90 / 100 responses will be analyzed at each time point using the Cochran-Mantel-Haenszel test to compare secukinumab and placebo, adjusting for body weight (<90 kg, ≥90 kg) (Stokes, Davis, and Koch, 2012). A 95% confidence interval for the difference between the two treatment groups in the proportion of subjects who are responders will be calculated using the normal approximation to the binomial distribution. For response (yes, no) at Week 12 (and other time points), a subject with a missing assessment will be considered as a responder (yes) if the subject meets the response criterion at the time of premature discontinuation from the study. Otherwise, the subject will be considered as a non-responder (no).

Analyses of the secondary efficacy variables will be based on the Full Analysis Set.

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 (e.g., vital signs and special tests) will be considered, as appropriate.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of subjects 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 the Week 12 visit will be included in the database for the analysis at the primary analysis time point (Week 12).

Laboratory variables will be summarized.

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

[redacted]

9.5.3 Resource utilization

Not applicable

9.5.4 Pharmacokinetics

Not applicable.

9.5.5 Pharmacogenetics/pharmacogenomics

Not applicable.

9.5.6 Other biomarkers

Not applicable.

9.5.7 PK/PD

Not applicable.

9.6 Interim analyses

The primary analysis at Week 12 is considered an interim analysis. As Week 12 is the primary analysis time point, no adjustment to the significance level of 0.05 will be made.

9.7 Sample size calculation

The sample size was based on change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio (TBR) from the aorta. Using a t-test, a clinically important mean treatment difference of 0.15, a (common) standard deviation (SD) of 0.196, an allocation ratio of 1:1, a two-sided significance level of 0.05, and a power of 0.90, it was determined that approximately 74 subjects (37 in each treatment group) are necessary (nQuery Advisor 7.0) (Bissonnette et al 2013; Tawakol et al 2013). Without adjusting for multiplicity, the sample size of 74 subjects will also provide at least 0.90 power for other biomarkers (see Section 6.4.2) if the treatment difference is 0.76 SD or smaller. The general threshold for clinical importance is 1 SD. Allowing for a loss to follow-up rate of 0.10, approximately 84 subjects (42 in each treatment group) will be randomized.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented 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 21 CFR, and Japanese Ministry of

[redacted]

Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should 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 (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

Novartis will provide to Investigators in a separate document a proposed informed consent form that complies with the ICH GCP 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 monitor after IRB/IEC approval.

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

10.3 Responsibilities of the investigator and IRB/IEC

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

[redacted]

10.4 Publication of study protocol and results

Novartis assures that 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.

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 subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an Investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

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. All significant protocol deviations will be recorded and reported in the CSR.

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 subjects may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring should be followed.

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[redacted]

13 Appendices

13.1 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests. Notable values for blood pressure and pulse are presented in Section 6.5.2.

Whether or not any action needs to be taken to address notable laboratory or vital signs 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.

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 and electrolyte variables

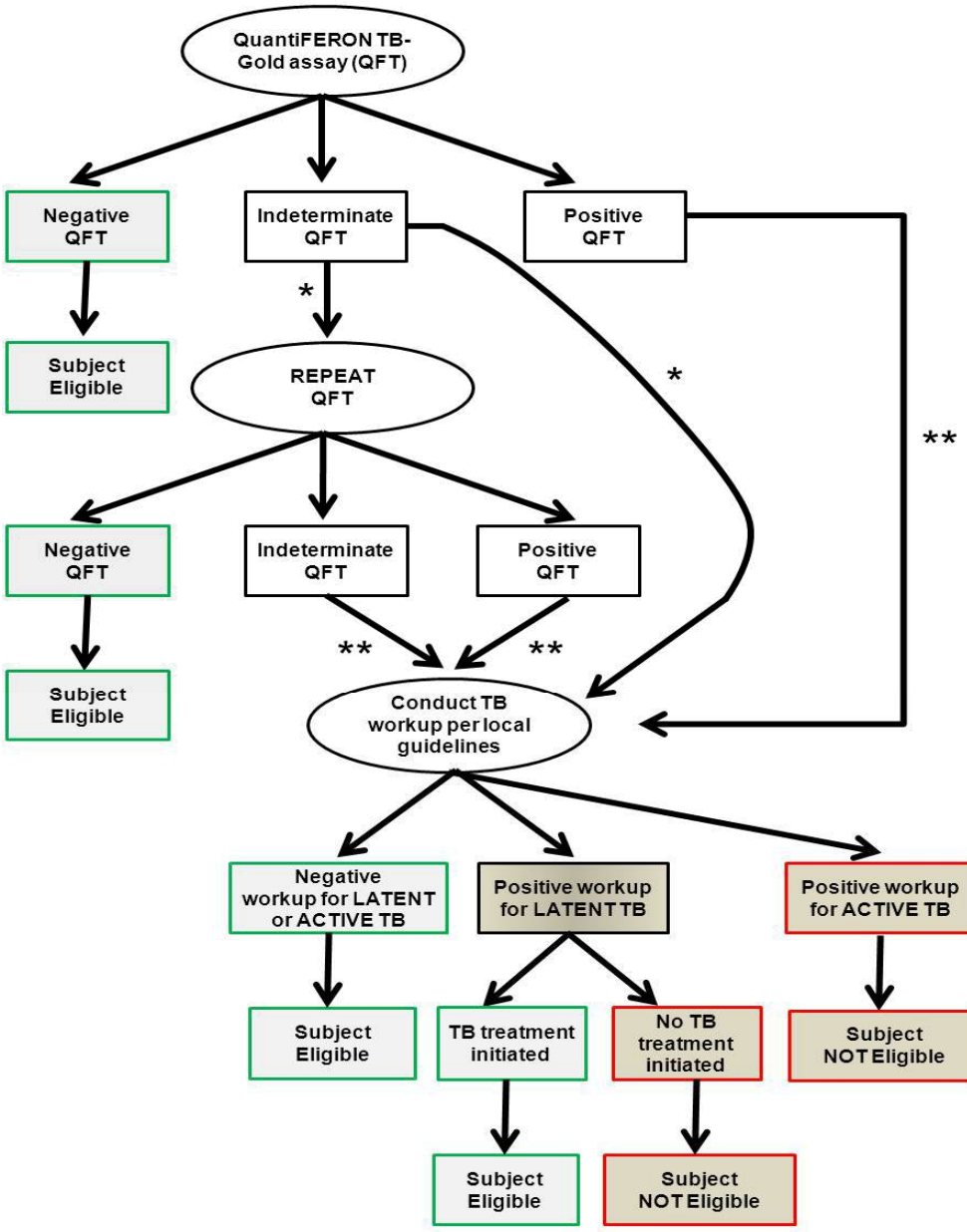
Creatinine (serum)	> 1.5 x ULN

Hematology values

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]

13.2 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).

13.3 Appendix 3: 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]

13.4 Appendix 4: Investigator's Global Assessment (IGA mod 2011)

Score	Detailed description
0 = Clear	No signs of psoriasis. Post inflammatory hyperpigmentation may be present
1 = Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling
2 = Mild disease	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling
3 = Moderate disease	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling
4 = Severe disease	Bright to deep dark red coloration; severe thickening with hard edges; severe/coarse scaling covering almost all or all lesions

[redacted]

13.5 Appendix 5: Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

[redacted]

6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

[redacted]