NOVARTIS

Global Clinical Development - General Medicine

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457A2324 / NCT03504852

A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of sub-cutaneous secukinumab in subjects of body weight 90 kg or higher with moderate to severe chronic plaque-type psoriasis

Document type:	Clinical Trial Protocol
EUDRACT number:	2015-004620-60
Version number:	00 (Original Protocol)
Clinical trial phase:	IIIB
Release date:	18-Dec-2017

Clinical Trial Protocol Template Version 3.2 (July 2016)

[redacted]

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
Alb	Albumin
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical (ATC)
BDR	Bioanalytical Data Report
β-hCG	β-subunit of hCG gonadotropin
BSA	Body Surface Area
CD	Cluster of differentiation
CFR	US Code of Federal Regulations
CHMP	Committee for medicinal products for human use
[redacted]	[redacted]
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CS	Corticosteroid
CT	Computerized tomography
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
e.g.	Exemplī grātiā (for example)
EOT	End of treatment
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
hCG	Human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
i.e.	of id est (in other words)
IEC	Independent Ethics Committee
[redacted]	[redacted]
IGA	Investigator's Global Assessment
IGA mod	Investigator's Global Assessment modified
IL	Interleukin

i.v.	Intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LFT	Liver function test
LLN	Lower Limit of Normal
MedDRA	Medical dictionary for regulatory activities
MI	multiple imputation
MRI	Magnetic resonance imaging
PASI	Psoriasis Area and Severity Index
PEA	Primary endpoint analysis (PEA)
PFS	pre-filled syringes
[redacted]	[redacted]
[redacted]	[redacted]
Q2 / Q2W	Every 2 weeks
Q4 / Q4W	Every 4 weeks
QFT	QuantiFERON TB-Gold test
SAE	Serious Adverse Event
s.c.	subcutaneously
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
TB	Tuberculosis
TBL	Total bilirubin
TNFα	Tumor necrosis factor alpha
USA	United States of America
UK	United Kingdom
ULN	Upper Limit of Normal
UV	Ultraviolet
WBC	White blood cells
WoCBP	Women of child bearing potential

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease.
[redacted]	
PASI 90 response	Subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline
[redacted]	
Patient/subject ID	A unique number assigned to each subject upon signing the informed consent
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
[redacted]	
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a

	spreadsheet or even hard-coded data.
Study drug/ treatment	Any single drug or combination of drugs administered to the subject as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CAIN457A2324
Full Title	A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of sub-cutaneous secukinumab in subjects of body weight 90 kg or higher with moderate to severe chronic plaque-type psoriasis
Brief title	Study of efficacy and safety of 2 secukinumab dose regimens in subjects of body weight 90 kg or higher with moderate to severe chronic plaque-type psoriasis
Sponsor and Clinical Phase	Novartis, Phase 3B
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to compare efficacy, safety and tolerability of secukinumab 300 mg every 2 weeks to secukinumab 300 mg every 4 weeks in subjects with moderate to severe chronic plaque-type psoriasis and body weight of 90 kg or higher. This study addresses a post-marketing commitment to the FDA (USA).
Primary Objective(s)	To demonstrate the efficacy of secukinumab 300 mg every 2 weeks in comparison to secukinumab 300 mg every 4 weeks with respect to PASI 90 response at Week 16
Secondary Objectives	To demonstrate the efficacy of secukinumab 300 mg every 2 weeks in comparison to secukinumab 300 mg every 4 weeks with respect to Investigator's Global Assessment (IGA) mod 2011 0 or 1 response at Week 16. To investigate the clinical safety and tolerability of secukinumab 300 mg every 2 weeks in comparison to secukinumab 300 mg every 4 weeks
Study design	This is a 52-week multicenter, randomized, double-blind, parallel-group trial in approximately 330 subjects with moderate to severe chronic plaque-type psoriasis of body weight 90 kg or higher at time of randomization. The study consists of 4 periods: screening (up to 4 weeks), treatment Period 1 (16 weeks), treatment Period 2 (36 weeks), and post-treatment follow-up (8 weeks). Subjects will be randomized using a 1:1 ratio to the following groups: Secukinumab 300 mg every 2 weeks; Secukinumab 300 mg every 4 weeks. [redacted]
Population	The study population will consist of approximately 330 adult male and female subjects (≥ 18 years old) with moderate to severe chronic plaque-

	type psoriasis of body weight of ≥ 90 kg at randomization.
Key Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations. 2. Subjects must be able to understand and communicate with the investigator and comply with the requirements of the study. 3. Men or women at least 18 years of age at time of screening. 4. Body weight of ≥ 90 kg at the time of randomization. 5. Chronic plaque-type psoriasis present for at least 6 months and diagnosed before randomization. 6. Moderate to severe psoriasis as defined at randomization by: • Psoriasis Area and Severity Index (PASI) score of 12 or greater, and • IGA mod 2011 score of 3 or greater (based on a static scale of 0 – 4), and • Body Surface Area (BSA) affected by plaque-type psoriasis of 10% or greater. 7. Candidate for systemic therapy. This is defined as a subject having moderate to severe chronic plaque-type psoriasis that is inadequately controlled by: • topical treatment and/or, • phototherapy and/or, • previous systemic therapy.
Key Exclusion criteria	1. Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis) at screening or Randomization. 2. Ongoing use of prohibited treatments. Washout periods detailed in the protocol have to be adhered to (Table 5-1). Subjects not willing to limit UV light exposure (e.g., sunbathing and / or the use of tanning devices) during the course of the study will be considered not eligible for this study since UV light exposure is prohibited. Note: administration of live vaccines 6 weeks prior to Randomization or during the study period is also prohibited. 3. Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting Interleukin-17 (IL-17) or the IL-17 receptor. 4. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 4 weeks until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations. 5. Pregnant or nursing (lactating) women 6. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no

	evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed). 7. History of hypersensitivity to any of the study drug constituents.
Study treatment	• Secukinumab 150 mg solution for sub-cutaneous injection in a 1 ml pre-filled syringe • Placebo solution for sub-cutaneous injection in a 1 ml pre-filled syringe
Efficacy assessments	• Investigator's Global Assessment for general psoriasis (IGA mod 2011; scale from 0 – 4) • Psoriasis Area and Severity Index (PASI; score from 0 – 72) [redacted]
Key safety assessments	• Evaluation of all AEs and SAEs • Physical examination • Vital signs • Height and weight • ECG • Laboratory evaluations (e.g. hematology, clinical chemistry, urinalysis) [redacted] • Pregnancy
[redacted]	[redacted]
Data analysis	The hypotheses will be tested sequentially and are included in a hierarchical testing strategy. Type-I-errors are set to keep a family-wise type-I-error of 2.5% (one-sided): H_1: secukinumab 300 mg every 2 weeks is not superior to secukinumab 300 mg every 4 weeks with respect to PASI 90 response at Week 16. H_2: secukinumab 300 mg every 2 weeks is not superior to secukinumab 300 mg every 4 weeks with respect to IGA mod 2011 0 or 1 response at Week 16. The testing sequence will continue to H_2 at α (one-sided) only if H_1 has been rejected. The primary analysis method will be the logistic regression with treatment group, and baseline weight, baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons between treatment arms utilizing the logistic regression model fitted. In case of response rates of 0% or of 100% in one of the treatment groups, Fisher's exact test will be applied. Confidence intervals for risk difference will be provided. Multiple imputation method will be used for handling missing data.
Key words	psoriasis, PASI, IGA mod 2011, secukinumab, pre-filled syringes

1 Introduction

1.1 Background

Psoriasis is a chronic relapsing disease of the skin characterized by variable clinical features. The lesions are classified as erythrosquamous, which indicates that both the vasculature (erythema) and the epidermis (increased scale formation) are involved.

Plaque-type psoriasis (also called plaque or chronic plaque psoriasis) is the most frequent clinical presentation and therefore, also called psoriasis vulgaris. The erythematous plaques are well defined with sharp borders. The silvery grey scale on the surface of the lesions is easily removed. Sharply demarcated lesions can present on the extensor surfaces of the knees and elbows and on the trunk. Lesions are often symmetrically distributed. The size of the lesions is highly variable. Psoriasis may also occur on the scalp, palms and/or soles (palmoplantar psoriasis), nails and in skin folds (intertrigo psoriasis). The amount of psoriasis covering the body can be measured roughly as a percentage of body surface area, using the handprint to represent 1% of the body surface. In approximately one-third of patients, more than 10% of the body is covered, and this is termed moderate to severe psoriasis. Clinical disease can also be assessed by a trained health-care practitioner, using the Psoriasis Area and Severity Index (PASI) score. This tool ranks severity of erythema (redness), induration (thickness), and desquamation (scale) and area affected by the plaques in different body sections, with 72 as the maximal score. PASI score of at least 12 is usually required to classify for moderate to severe psoriasis.

Treatment of moderate to severe psoriasis was based on phototherapy, conventional systemic treatment (e.g. methotrexate, cyclosporine, acitretin) and biologics (tumor necrosis factor alpha (TNFα)-inhibitors etanercept, infliximab and adalimumab).The primary indication for these biological products is the treatment of moderate to severe psoriasis not responding satisfactorily to phototherapy and conventional systemic treatment such as methotrexate or acitretin.

Extensive clinical experience with TNFα-inhibitors has been collected over the past 10 years and these agents are generally considered to be effective and relatively safe (Papp et al 2006). However, a substantial percentage of patients do not respond well to treatment with TNFα-inhibitors. This inadequate response may imply either a primary failure (e.g. not achieving a decrease in Psoriasis Area and Severity Index (PASI) score of at least 50% after adequate duration of treatment), secondary failure (an initially adequate response that is lost over time) or intolerance for the TNFα-inhibitor. The percentage of patients with an inadequate response to TNFα-inhibitors can be as high as 40 to 60% (van Lümig et al 2010).

The arrival of a new class of systemic, biological drugs such as ustekinumab (interleukin (IL)-12/23 inhibitor) has provided clinicians with more treatment options. Ustekinumab has shown good clinical efficacy in a number of well-designed Phase 3 studies (Papp et al 2008). PASI response rates were better than those of etanercept and comparable to PASI response rates of infliximab and efficacy was generally maintained up to 3 years after initiation of treatment (Kimball et al 2012). Additionally, a number of IL-17A and IL-17RA inhibitors are investigated for the treatment of a range of immune mediated inflammatory diseases.

Secukinumab (AIN457) is a recombinant high-affinity fully human monoclonal anti-human IL-17A antibody of the immunoglobulin (Ig) G1/κ-class. Secukinumab binds to human IL-17A and neutralizes the bioactivity of this cytokine. IL-17A is the central cytokine of a newly defined subset of inflammatory T cells, the Th17 cells which, in several animal models, are pivotal in multiple autoimmune and inflammatory processes. IL-17A is mainly produced by memory effector CD4+ and CD8+ T lymphocytes and is being recognized as one of the principal pro-inflammatory cytokines in immune mediated inflammatory diseases. Its neutralization is expected to treat the underlying pathophysiology of immune mediated disease, and as a consequence provide relief of psoriatic symptoms. Secukinumab has been shown to be superior to etanercept (Langley et al 2014) and superior to ustekinumab (Thaci et al 2015) in clearing skin of subjects with moderate to severe psoriasis with comparable safety profile.

Secukinumab (Cosentyx®) was approved in 2014 in Japan, in 2015 in the US (FDA 2014), in the European Union (EU), in Switzerland and in other countries for the treatment of moderate to severe plaque psoriasis in adults, with a recommended dose of 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. Secukinumab is available as a powder for solution for injection, and as a solution of 150 mg in 1 mL for injection in pre-filled syringe or pre-filled pen. Currently two injections are required for the administration of the recommended dose.

As of 25 Jun 2017, over 11,000 subjects (healthy subjects and patients) have received secukinumab in Novartis sponsored clinical studies at doses ranging from 0.1 mg/kg to 30 mg/kg intravenously (i.v.), and from 25 mg to 300 mg subcutaneously (s.c.), given as single or multiple doses. Full safety results including all reported AEs are currently available for completed studies across different indications. In general, these results show comparable numbers of adverse events (AEs) in subjects treated with secukinumab compared to placebo without indication of any specific organ toxicity. The Investigator's Brochure (IB) provides a more detailed review of the pre-clinical and clinical information on secukinumab.

1.2 Purpose

The purpose of this study is to compare efficacy, safety and tolerability of secukinumab 300 mg every 2 weeks to secukinumab 300 mg every 4 weeks in subjects with moderate to severe chronic plaque-type psoriasis and body weight of 90 kg or higher, [redacted]

This study addresses a post-marketing commitment to the FDA (USA). Refer to Section 3.2 for detail on commitment.

2 Study objectives and endpoints

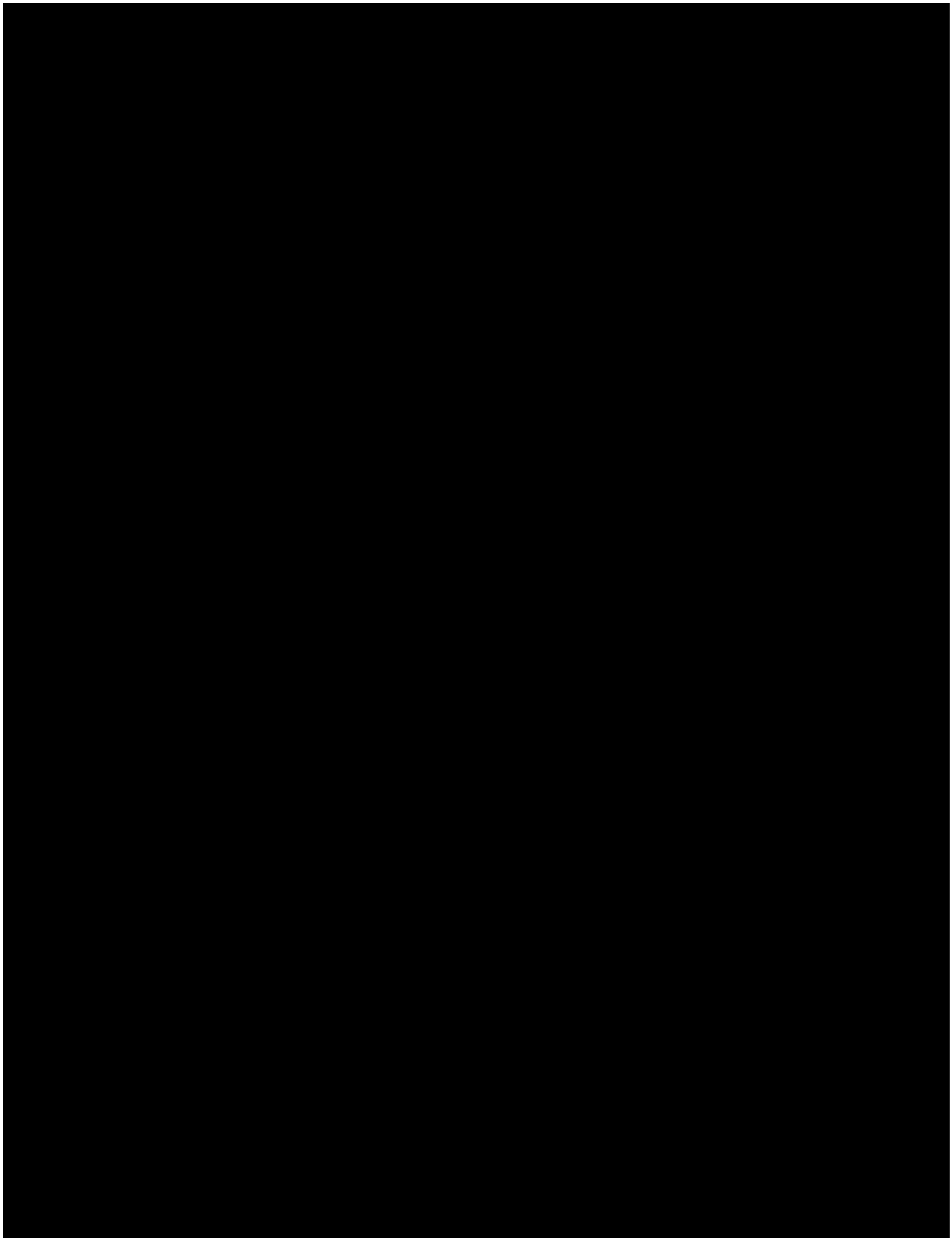
2.1 Objectives and related endpoints

The objectives and related endpoints presented in Table 2-1 will be evaluated in subjects with body weight of 90 kg or higher at randomization and with moderate to severe chronic plaque-type psoriasis.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To demonstrate the efficacy of secukinumab 300 mg every 2 weeks in comparison to secukinumab 300 mg every 4 weeks with respect to PASI 90 response at Week 16	Endpoint: PASI 90 response Description: Percentage of subjects who achieve ≥ 90% reduction in PASI score compared to baseline Time frame: 16 weeks
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
To demonstrate the efficacy of secukinumab 300 mg every 2 weeks in comparison to secukinumab 300 mg every 4 weeks with respect to Investigator's Global Assessment (IGA) mod 2011 0 or 1 response at Week 16.	Endpoint: IGA mod 2011 0 or 1 response Description: Percentage of subjects who achieve IGA mod 2011 0 or 1 and improved by at least 2 points on the IGA scale compared to baseline. Time frame: 16 weeks
To investigate the clinical safety and tolerability of secukinumab 300 mg every 2 weeks in comparison to secukinumab 300 mg every 4 weeks	Endpoint: Clinical safety and tolerability. Measure: vital signs, clinical laboratory variables, ECGs, Adverse Events monitoring Time frame: up to 52 weeks

[redacted]



3 Investigational plan

3.1 Study design

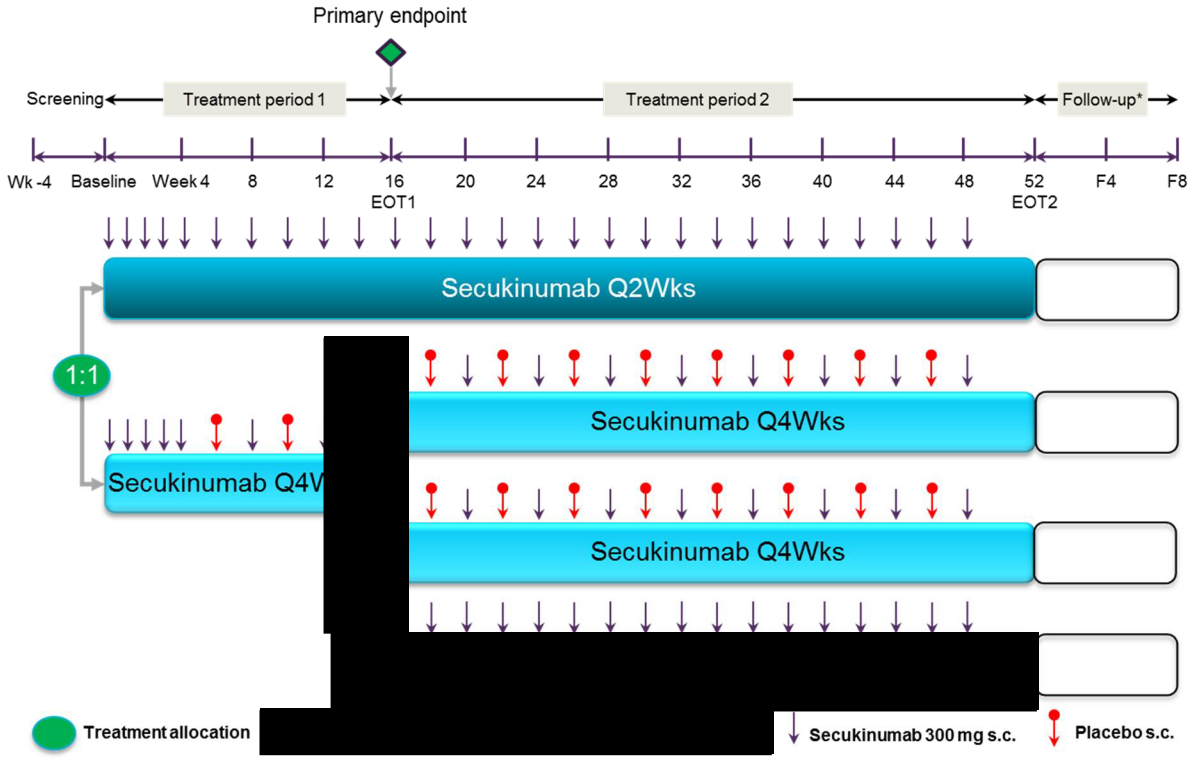
This is a 52-week multicenter, randomized, double-blind, parallel-group trial in approximately 330 subjects with moderate to severe chronic plaque-type psoriasis of body weight 90 kg or higher at time of randomization.

The study consists of 4 periods: screening (up to 4 weeks), treatment Period 1 (16 weeks), treatment Period 2 (36 weeks), and follow-up (8 weeks).

Safety, efficacy, [redacted] of secukinumab will be performed.

An outline of the study design is presented in Figure 3-1 and a detailed visit and assessment schedule in Table 6-1.

Figure 3-1 Study design



EOT1/2: End of treatment 1/2 Q2Wks/Q4Wks: Every 2/4 weeks

Screening Period (Screening to Randomization)

The screening period of at least 1 week and up to 4 weeks will be used to assess the subject's eligibility and to taper subjects off prohibited medications.

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

The Treatment Period 1 is the period from randomization (baseline) through Week 16 prior to dosing. At the start of treatment Period 1, eligible subjects will be randomized via Interactive Response Technology (IRT) using a 1:1 ratio to one of the following treatment groups:

- Secukinumab 300 mg every 2 weeks
- Secukinumab 300 mg every 4 weeks

Refer to Section 5.2 for details on treatment arms.

All subjects will receive 2 injections of secukinumab 150 mg once weekly for four weeks (at Randomization, weeks 1, 2 and 3). Thereafter the frequency of secukinumab/placebo injections will be as per the treatment groups assigned at baseline. To maintain the treatment blind, subjects assigned to receive secukinumab 300 mg every 4 weeks will also receive two placebo injections (2 x secukinumab placebo 150 mg s.c.) every 4 weeks starting at Week 6 (see Figure 3-1).

Subjects who complete treatment Period 1 will enter treatment Period 2. For all subjects who discontinue study treatment prematurely for any reason before the End of Treatment Period 1/Week 16 visit (EOT 1), an EOT 1 visit should be performed approximately four weeks after their last dose of study drug and then subjects should enter the treatment free follow-up period.

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

Treatment Period 2 is the period from Week 16 through Week 52. The Week 16 dose is the first dose of the treatment Period 2 and the last dose will be administered at Week 48.

- Subjects from the 300 mg every 2 weeks group will remain on secukinumab 300 mg every 2 weeks until the end of treatment
- Subjects from the 300 mg every 4 weeks group:

This allocation will be based on a pre-assignment done at the randomization/baseline visit.

The planned end of treatment period 2 visit (EOT 2) will be performed at Week 52.

For all subjects who discontinue study treatment prematurely for any reason before the end of treatment period 2/Week 52 (EOT2), an EOT2 visit should be performed approximately 4 weeks after their last dose of study drug and then subjects should enter the post treatment follow-up period.

Post treatment follow-up period

All subjects should enter the post treatment follow-up period, which includes the F4 and F8 follow-up visits. No study treatment (secukinumab) is administered during this period. Follow-up visit F4 is approximately 4 weeks after the EOT 1/EOT 2 visit and 8 weeks after last study treatment administration. Follow-up visit F8 is approximately 8 weeks after the EOT 1/EOT 2 visit, and 12 weeks after the last study treatment administration.

3.2 Rationale for study design

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

This study is a post approval commitment to the United States Food and Drug Administration (FDA). The FDA requested a clinical trial to:

- evaluate the treatment effect and safety profile of a higher exposure of secukinumab in psoriasis subjects with higher body weight and

The request was based on the FDA's exposure-response analysis which suggested that IGA 0/1 response rate in subjects with body weight ≥ 90 kg administered 300 mg may be further increased if exposures are increased

The randomized, double-blind, parallel-group design of this study is aligned with previous studies performed in the indication of plaque psoriasis and registration secukinumab studies.

The blinding will be maintained throughout the study to ensure reliable efficacy and safety measures of the 300 mg every 2 weeks regimen and its comparison to the 300 mg every 4 weeks regimen.

The primary endpoint is PASI 90 assessed at Week 16. PASI 90 was chosen as the primary efficacy variable to represent the therapeutic goal recognized by the American Academy of Dermatology and European Medicines Agency as "measure of optimal response" or "treatment success". By Week 16 subjects would have the greatest chance of reaching maximum efficacy with secukinumab therapy, as established in the registration Phase 3 studies (PASI 90 response was around 70%).

The study's design, with a total treatment duration of 52 weeks, will allow assessment of long term efficacy and safety of the two dose regimens and is aligned with previous studies performed in the indication of plaque psoriasis and registration secukinumab studies.

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

Secukinumab 300 mg s.c. with an initial weekly induction schedule up to 4 weeks followed by a s.c administration of every four weeks up to Week 48 is based on the secukinumab Phase 3 registration program.

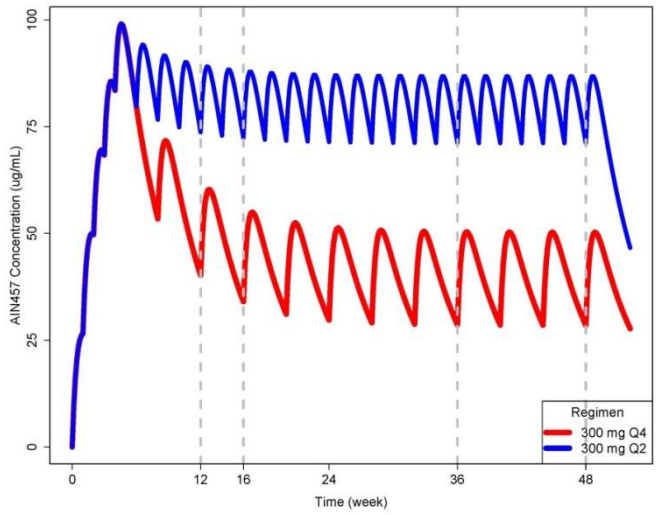
A higher monthly dose regimen than the one approved for the psoriasis indication has been included in the study as requested by FDA. This higher monthly dose regimen is being assessed to see if improvement in response is achievable in subjects with body weight ≥ 90 kg, while maintaining a favorable safety profile.

Systemic exposure varies with body weight in an allometric relationship. For clearance, the allometric exponent was estimated to be close to 1; in other words, a doubling of body weight could lead to a nearly 2-fold increase in clearance and therefore reduced serum exposure (Bruin et al 2017). Therefore, evaluation of a dosing regimen with higher exposure than resulting from the marketed regimen is appropriate in this heavier subject population.

Based on a large database of Phase II and Phase III double-blind randomized placebo-controlled studies including 1,405 subjects treated with secukinumab, a clear dose/exposure response relationship was established. Serum secukinumab concentration was by far the most important predictor of efficacy.

As shown in Figure 3-2, which presents predicted secukinumab concentration based on population pharmacokinetics models in psoriasis, shows that increasing the dose regimen from 300 mg every 4 weeks to 300 mg every 2 weeks after the induction period would result in a sustained higher secukinumab serum concentration.

Figure 3-2 Predicted systemic exposure with secukinumab 300 mg given every 2 weeks or every 4 weeks during maintenance



300 mg Q4: secukinumab 300 mg weekly for 5 weeks (induction), then every 4 weeks (maintenance)
300 mg Q2: secukinumab 300 mg weekly for 5 weeks (induction), then every 2 weeks (maintenance)

Therefore the hypothesis to be tested in this study is that increasing the exposure to secukinumab in subjects with higher weight (i.e. ≥ 90 kg) would result in higher percentage of subjects achieving PASI 90 at Week 16.

Risk benefit evaluation of the proposed doses are presented in Section 3.6, Risk and benefits.

3.4 Rationale for choice of comparator

This study will compare a higher dose regimen (i.e. 300 mg every 2 weeks) which could potentially bring improvement in response while maintaining a favorable safety profile versus secukinumab 300 every 4 weeks, which is the approved dose regimen for psoriasis patients.

3.5 Purpose and timing of primary endpoint analysis/design adaptations

A primary endpoint analysis (PEA) may be conducted when all subjects have completed the Week 16 visit at which the primary endpoint is assessed. Additional analyses may be performed to support health authority interactions as necessary.

3.6 Risks and benefits

Secukinumab (Cosentyx) with a recommended dose of 300 mg every 4 weeks was approved in 2014 in Japan, in 2015 in the US, in the EU, in Switzerland and other countries for the treatment of adults with moderate to severe plaque psoriasis. Secukinumab 150 mg is available as a powder for solution for injection, and as a solution for injection in pre-filled syringe or pre-filled pen.

Non-clinical studies and Phase 2 and 3 clinical studies in adults have not shown any impediment to using secukinumab subcutaneously in human. As of 25 Jun 2017, over 11,000 patients and healthy volunteers received secukinumab treatment in Novartis sponsored investigational clinical studies, including approximately 5,865 patients with moderate to severe plaque psoriasis.

In adult studies, secukinumab has shown an excellent efficacy profile in the treatment of moderate to severe chronic plaque psoriasis. Superiority of secukinumab 300 mg to placebo was demonstrated for the co-primary efficacy criteria of PASI 75 and IGA mod 2011 0 or 1 at 12 weeks in all 4 pivotal placebo-controlled trials (> 62% for PASI 75 and > 48% for IGA mod 2011 0 or 1). Etanercept and placebo-controlled Studies CAIN457A2302 and CAIN457A2303 have shown the superior efficacy of secukinumab 300 mg compared to etanercept and placebo with a rapid onset of action, while Study CAIN457A2317 showed superiority and sustained long-term efficacy of secukinumab 300 mg versus ustekinumab in patients with moderate to severe plaque-type psoriasis.

Potential risks for subjects are as outlined in the approved product labelling. At this time, safety data including (1) AE data, laboratory parameters, available immunogenicity data from the completed studies, and (2) SAE data from the Phase 3 studies do not show any other safety risk apart from the approved safety profile. The safety data from the completed and ongoing studies demonstrate a good safety profile which includes an observed risk of infections in particular candida infections and neutropenia or hypersensitivity reactions that can be seen with administration of foreign proteins. Most of the infections were non-serious,

mild to moderate in severity, clinically easily manageable and did not lead to treatment discontinuation. Cases of neutropenia were uncommon, generally mild to moderate and transient and did not lead to treatment discontinuation, and only a few cases were temporally associated with non-serious infections.

Subjects with pre-existing malignancies within the past 5 years are generally excluded from studies with secukinumab although no signals have been observed that would suggest that secukinumab would increase the risk for malignancies.

Based upon the results of the toxicology studies demonstrating lack of effect of secukinumab on fertility and embryo-fetal development, women of child bearing potential (WoCBP) can be included in studies with secukinumab, but pregnancy should be avoided by proven effective measures. No contraceptive measures are required for males participating in studies with secukinumab.

Secukinumab 300 mg s.c. every 2 weeks was administered in 5 completed studies. For two of these studies (CAIN457C2302 and CAIN457A2208) the number of subjects was low (<10) and therefore these are not further discussed here.

Patients with uveitis received secukinumab 300 mg s.c. every 2 weeks for up to 50 weeks in Study CAIN457C2301/C2301E1 and up to 44 weeks in Study CAIN457C2303/2303E1.

Table 3-1 Exposure to 300 mg s.c. every 2 weeks in completed trials

Study (Indication)	Average weight (kg)	Number of subjects exposed for:		
		Any duration	6 months	1 year
CAIN457C2301& CAIN457C2301E1 (Uveitis)	79.4	29	21	4
CAIN457C2303& CAIN457C2303E1 (Uveitis)	69.8	39	34	0

In Study CAIN457C2301/C2301E1, the overall number of subjects with an adverse event was similar between subjects who received secukinumab 300 mg every 2 weeks versus those who received placebo at the same frequency (82.8% versus 84.8% respectively), while in Study CAIN457C2303/2303E1, the overall frequency of AE was higher in the secukinumab 300 mg every 2 weeks group compared to placebo (82.1% versus 74.4% respectively). Long-term treatment with more frequent s.c. doses of secukinumab (300 mg every 2 weeks) was associated with a numerical increase in infections, mainly due to more reports of non-serious nasopharyngitis, influenza, and upper respiratory tract infection in both studies. The sample size for the secukinumab 300 mg every 2 weeks were relatively small in these studies and interpretation of these results must therefore be done with caution.

Secukinumab 300 mg s.c. every 2 weeks was also administered in one ongoing study for which the results are available. Study CAIN457ADE04 is a randomized, double blind, multicenter study to assess the efficacy and safety of 16 weeks secukinumab dosage interval shortening (2 weekly 300 mg s.c.) in comparison to continued standard treatment (4 weekly 300 mg s.c.) in patients with moderate severe plaque type psoriasis who achieved less than clear or almost clear skin (PASI response greater than or equal to 75 to PASI less than 90) after 16 weeks under the standard dose of secukinumab. A total of 772 subjects were enrolled

into the selection phase of the study, then 325 subjects were randomized to either secukinumab every 4 weeks (N=162) or every 2 weeks (N=163).

Within the randomized subjects, there was a lower incidence rate of AEs in the 300 every 2 weeks arm compared to the 300 mg every 4 weeks arm (12.9% and 16.7%, respectively). The majority of the AEs were from the SOC infections and infestations (10.5%), with mild or moderate nasopharyngitis as the primary contributor (3.1%). An increase in candida infection rate was observed in the 300 mg every 2 weeks arm (3.1%) as compared to the 300 mg every 4 weeks arm (1.2%). Serious adverse events occurred at comparable rates to other secukinumab studies. SAEs occurred less frequently in the 300 mg every 2 weeks arm, and were also less often related in this arm than in the 300 mg every 4 weeks arm (2.5% and 4.9%, respectively). The most common SOC was infections and infestations (1.2%); 4 of the 5 reported serious infections were assessed as related to study treatment. AEs and SAEs lead to permanent discontinuation of study treatment in the 300 mg every 4 weeks only (0.9%), and to interruption of study treatment less frequently in the 300 mg every 2 weeks arm than in the 300 mg every 4 weeks arm (0.6% and 2.5%, respectively). Results from this study showed no unexpected safety signals in the safety profile of secukinumab at both doses regimens.

4 Population

The study population will consist of a representative group of adult male and female subjects (≥ 18 years old) with moderate to severe chronic plaque-type psoriasis of body weight of ≥ 90 kg at randomization. It is aimed to randomize a total of approximately 330 subjects in approximately 100 study sites worldwide. Approximately 472 subjects (30% projected screen failure rate) are expected to be screened to provide the 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 must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed. Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations.
2. Subjects must be able to understand and communicate with the investigator and comply with the requirements of the study.
3. Men or women at least 18 years of age at time of screening.
4. Body weight of ≥ 90 kg at the time of randomization.
5. Chronic plaque-type psoriasis present for at least 6 months and diagnosed before randomization.
6. Moderate to severe psoriasis as defined at randomization by:
   - PASI score of 12 or greater, and
   - IGA mod 2011 score of 3 or greater (based on a static scale of 0 – 4), and
   - Body Surface Area affected by plaque-type psoriasis of 10% or greater.
7. Candidate for systemic therapy. This is defined as a subject having moderate to severe chronic plaque-type psoriasis that is inadequately controlled by:

- topical treatment and/or,
- phototherapy and/or,
- previous systemic therapy.

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. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 4 weeks until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations.
2. History of hypersensitivity to any of the study drug constituents.
3. Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis) at screening or Randomization.
4. Drug-induced psoriasis (i.e., new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium) at Randomization.
5. Ongoing use of prohibited treatments. Washout periods detailed in the protocol have to be adhered to (Table 5-1). Subjects not willing to limit UV light exposure (e.g., sunbathing and / or the use of tanning devices) during the course of the study will be considered not eligible for this study since UV light exposure is prohibited.

   Note: administration of live vaccines 6 weeks prior to Randomization or during the study period is also prohibited.
6. Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor.
7. Pregnant or nursing (lactating) women
8. Women of child-bearing potential (WoCBP), defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g. in EU 20 weeks).

   Basic contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy [with or without hysterectomy], total hysterectomy or tubal ligation at least six weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For United Kingdom: with spermicidal foam/gel/film/cream/vaginal suppository.

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

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

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

  Note: Women are considered post-menopausal and not of 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 have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.

9. Active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of secukinumab therapy. Also, underlying conditions (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. In addition, current severe progressive or uncontrolled diseases which renders the subject unsuitable for the trial or puts the subject at increased risk, including any medical or psychiatric condition which, in the Investigator’s opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
10. Presence of investigator identified significant medical problems which at investigator's discretion will prevent the subject from participating the study, including but not limited to the following:
    - Subjects with severely reduced kidney function (estimated glomerular filtration rate (eGFR) ≤29 ml/min/1.73m2)
11. Chest X-ray, computerized tomography (CT scan), or Magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process, obtained within 12 weeks prior to randomization, and evaluated by a qualified physician.
12. Active systemic infections during the last two weeks (exception: common cold) prior to randomization or any infection that reoccurs on a regular basis.
13. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold test (QFT) at screening. Subjects with a positive or indeterminate QFT test may participate in the study if full tuberculosis work up (according to local practice/guidelines) was completed within 12 weeks prior to randomization and establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local guidelines prior to randomization.

14. Past medical history record of infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C prior to Randomization.
15. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
16. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
17. History or evidence of ongoing alcohol or drug abuse, within the last six months before Randomization.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Novartis will supply the investigational therapy as follows:

- Secukinumab 150 mg solution for sub-cutaneous injection in a 1 ml pre-filled syringe
- Placebo solution for sub-cutaneous injection in a 1 ml pre-filled syringe

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

5.1.2 Additional treatment

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

5.2 Treatment arms

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

- **Secukinumab 300 mg every 2 weeks group**: subjects will receive 2 injections of secukinumab 150 mg once weekly for four weeks (at Randomization, Weeks 1, 2, and 3), followed by 2 injections of secukinumab 150 mg every two weeks, starting at Week 4 and up to Week 48.
- **Secukinumab 300 mg every 4 weeks group**: subjects will receive 2 injections of secukinumab 150 mg once weekly for four weeks (at Randomization, Weeks 1, 2, and 3), followed by 2 injections of secukinumab 150 mg every four weeks, starting at Week 4 and up to Week 12. In order to maintain the treatment blind, subjects will also receive 2 injections of secukinumab placebo every 4 weeks starting at Week 6, until Week 14.

[redacted]

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

5.3 Treatment assignment and randomization

The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the package of study drug to be dispensed to the subject. The randomization number will not be communicated to the caller.

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

Randomization will not be stratified.

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

5.4 Treatment blinding

Subjects, investigator staff and persons performing the assessments, and data analysts will remain blind to the identity of the study treatment from the time of randomization until the end of study database lock, using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:
   - Specific vendors whose role in trial conduct requires their unblinding (e.g., IRT)
   - Drug Supply Management

- The designated Novartis study team members involved in the primary endpoint analysis, as described in Section 5.4.1

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

Unblinding will only occur in the case of patient emergencies (see Section 5.6), at the time of the primary endpoint analysis after all patients have completed Week 16 (see Section 5.4.1) and at the conclusion of the study. The appropriate personnel from the study site and Novartis will assess whether the study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason (see Section 5.5.9).

[redacted]

5.4.1 Unblinding for primary endpoint analysis

If a primary endpoint analysis is performed after all patients have completed Week 16, a small selected group of team members (e.g. biostatisticians and programmers involved in the analysis, Medical Lead) may have access to the unblinded results. Subjects and site personnel directly involved in the conduct of the trial, i.e. investigator staff and persons performing the assessments, will remain blinded until the conclusion of the study to ensure study integrity is maintained.

5.5 Treating the patient

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

5.5.1 Patient numbering

Each subject is uniquely identified by a Subject Number assigned by Novartis. The Subject Number is composed of a site number and a sequential number. 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 available in electronic data capture (EDC) system. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT. The site must select the case report form (CRF) book with a matching Subject Number in the EDC system to enter data.

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

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to one of the 2 treatment arms and a specific visit.

Investigator staff will identify the study drug package(s) to dispense to the subject by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the subject, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

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

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. The subjects will record the date(s) of administration at home on a diary and will return the used medication and packaging at their next visit to the site. Subjects will be asked to return all unused medication and packaging the latest at the completion of the study or at the time of discontinuation of the investigational treatment. Site staff will record in the appropriate documents the dates of the administration. Detailed instructions will be provided separately. Patients/subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

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

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

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

Each subject will require one box of syringe set (PFS) per dose throughout the study:

- Two secukinumab 150 mg PFS **OR**
- Two secukinumab placebo 150 mg PFS.

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

Administration

All doses of study treatment that are administered at the study site should be performed after the study assessments for the visit, including blood sampling [redacted], have been completed.

The first study treatment administration will occur at the Randomization/baseline Visit, after all study scheduled assessments have been performed (and inclusion/exclusion criteria confirmed) and only after the scheduled blood samples have been drawn. Subjects will be asked to record details of the doses administered at home on a diary that will be returned to the sites at site visits for review and data capture by the site.

Prior to administration the boxes containing the PFSs with study treatment solution should be allowed to come to room temperature unopened before administration. Used PFSs should be disposed immediately after use in a sharps container **OR** according to the regulatory needs of the respective countries. For details please refer to the pharmacist manual.

The study treatment solution must be injected subcutaneously in non-affected areas of the skin. If possible, throughout the trial administer the study treatment to one of the following body regions, rotating the injection site from visit to visit: right thigh, left thigh, right stomach, left stomach, upper outer arm (when assisted by attendant).

All dates and times of injections during the study must be recorded on the appropriate CRF.

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

Home Administration

Between study visits, subject will be expected to perform home administration in order to have administration of study medication every 2 weeks. Home administration can be performed by subject or caregiver.

The following time points are planned for home administrations of study medication: Weeks 6, 10, 14, 18, 22, 26, 30, 34, 36, 38, 42, 44, 46 and 48.

At the randomization/baseline visit the subjects will be instructed by the site staff walking them through the “Instructions for Use” on how to self-inject via PFS. For subjects willing to self-inject, the first administration should be performed under guidance and supervision of a site staff member.

If the subject or caregiver is not able/confident to perform home administration, the subject will be allowed to return to the site for administration of the medication. However, during those visits no other assessments will be performed.

During home administration, subjects are expected to contact the investigator/site staff in case they are experiencing any AE/SAEs or have any concerns.

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

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

However, for patients who are unable to tolerate the protocol-specified dosing scheme, a dose interruption of investigational drug is permitted in order to keep the patient on study drug. A maximum of one dose may be missed during each period.

Dosing can be brought forward or delayed by up to 1 week. The subsequent dose should be given according to the original schedule (i.e., do not move subsequent dose dates).

These changes must be recorded on the appropriate CRF.

5.5.6 Rescue medication

Rescue medication for psoriasis is not permitted in this study.

5.5.7 Concomitant medication

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

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started.

5.5.8 Prohibited medication

Use of any treatments displayed in Table 5-1 that could confound the efficacy are NOT allowed during the study for any indication and wash-out periods for these treatments prior to randomization are indicated in the table. If the use of these treatments is required, then the subject should **NOT** be randomized into the study.

The investigator should instruct the subject to notify the study site 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 treatment with study treatment must be listed on CRF.

If a prohibited treatment listed in Table 5-1 was used during the study, the subject should discontinue use of the prohibited treatment if he/she wishes to continue in the study. At the discretion of the investigator, if the subject's use during the study of a prohibited treatment listed in Table 5-1 presents undue safety risk for the subject, the subject should be discontinued from study treatment as per Section 5.6.2. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

During the screening period, subjects will be allowed to use some active topical treatments for any indication in the following body regions: face, scalp, and genitoanal area. The active topical treatments are limited to: mild or moderate potency corticosteroid (CS). The subject must stop use of these topical CS at least 12 hours preceding the Randomization visit.

For all other body regions, a washout period of 2 weeks applies for all active topical treatments for any indication (Table 5-1).

Table 5-1 Prohibited medication

Prohibited treatments[1, 2]	**Washout period (before randomization)**	**Note** [1]If a prohibited treatment of psoriasis is used during the study, the subject should discontinue use of the prohibited treatment if he/she wishes to continue in the study. [2] In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator.
Alefacept, briakinumab, efalizumab, ustekinumab	24 weeks	
Biological immunomodulating agents other than above (e.g., adalimumab, etanercept, infliximab)	12 weeks	
Other systemic immunomodulating treatments (e.g., Methotrexate, cyclosporine A, corticosteroids, cyclophosphamide)	4 weeks	
Other systemic psoriasis treatments (e.g. retinoids, fumarates, apremilast)	4 weeks	
Photochemotherapy (e.g., psoralen and ultraviolet A (PUVA))	4 weeks	
Phototherapy (e.g., UVA, UVB)	2 weeks	
Topical treatment[3,4,5] that is likely to impact signs and symptoms of psoriasis (e.g., corticosteroids [CS], vitamin D analogues, pimecrolimus, tacrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tar, urea, α-hydroxy or fruit acids)	2 weeks	[3] Including intra-articular or peri-articular injections. Note that inhaled corticosteroids as well as corticosteroid drops in the eye or ear or nasal sprays are permitted. [4] Mild to moderate topical corticosteroids are allowed only during the screening period if used only on the face, scalp, hands and feet and/or genitoanal area and if not used during the 12 h preceding the randomization visit. [5] Topical corticosteroids and other topical treatments will be allowed during treatment period 2 only if (all must apply):

Prohibited treatments[1, 2]	**Washout period (before randomization)**	**Note**
		[1]If a prohibited treatment of psoriasis is used during the study, the subject should discontinue use of the prohibited treatment if he/she wishes to continue in the study. [2] In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator.
		•medication was started after the Week 16 visit was completed; •medication was used for 14 consecutive calendar days or less; •medication was used for an indication other than psoriasis and not on the area affected with psoriasis.
Live vaccinations[6]	6 weeks	[6] If the subject received a live vaccination during the study, the subject must discontinue study treatment.
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)	

There is no restriction on the use of anti-histamines and on the use of topical corticosteroids in the eye, nose or ear.

Exposure to light

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

5.5.9 Emergency breaking of assigned treatment code

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

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

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

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

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

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

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.

The information to be collected at this follow-up visit includes concomitant medications, adverse events, and survival status.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study drug is stopped earlier than the protocol planned duration.

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

The investigator/qualified site staff must discontinue study treatment for a given subject if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

If discontinuation occurs for any reason in a treatment period, 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 by investigator/qualified site staff on the disposition CRF. The investigator must also contact the IRT to register the subject's discontinuation from study treatment. If study drug discontinuation occurs because treatment code has been broken (emergency unblinding), please refer to Section 5.5.9.

Study treatment *must* be discontinued under the following circumstances:

- Subject wish
- Withdrawal of consent
- 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).
- Any laboratory abnormalities that in the judgment of the investigator/qualified site staff, and taking into consideration the subject's overall status, prevents the subject from continuing study treatment.
- Pregnancy (see Section 6.5.6 and Section 7.5)
- Use of prohibited treatment as per recommendations in Section 5.5.8.
- Any situation in which study participation might result in a safety risk to the subject
- Emergency unblinding

Subjects discontinued from study treatment will NOT be considered discontinued from the study. The subject should return to the site after discontinuation of study drug, for an End of Treatment (EOT) visit and Follow-up visits (F4 and F8). Assessments detailed in the "End of Treatment visit" and Follow-up visits (F4 and F8) in Table 6-1 should be completed and recorded in the CRF. The investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the CRF.

At the time of the study treatment discontinuation visit, if it has been approximately 4 weeks post last dose of study treatment then the assessments described at EOT1 Visit Week 16 (for early discontinuation during treatment Period 1) or EOT2 Visit Week 52 (for early discontinuation during treatment Period 2) should be completed at this visit.

If it has not been approximately 4 weeks post last dose of study treatment at the time of the study treatment discontinuation visit, then the subject should be scheduled to return 4 weeks post last dose for their EOT1or EOT2 visit as appropriate.

Discontinuation from the post-treatment follow-up period

If premature withdrawal occurs for any reason in the post treatment follow-up period, the investigator must make every effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the appropriate CRF of the corresponding period.

See Section 6 for the required assessments of these subjects who discontinue from the post-treatment follow-up period.

5.6.3 Withdrawal of informed consent

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

- Does not want to participate in the study anymore

AND

- Does not want any further visits or assessments

AND

- Does not want any further study related contacts

AND

- Does not allow analysis of already obtained biologic material

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

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment Table 6-1.

5.6.4 Loss to follow-up

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

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrollment). Should this be necessary, the subject must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator 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 study visits and indicates with an "X" when the assessments are to be performed. An 'S' indicates the data for that assessment are in the source documents at the site.

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

If for any reason the subject is a screen failure, the subject may be rescreened. There is no restriction on the number of times a potential subject may be rescreened or on how much time must pass from the date of screen failure and the date of rescreening.

If a subject rescreens for the study, then the subject must sign a new ICF and be issued a new subject number prior to any screening assessment being conducted for the subject under the new screening subject number. For all rescreened subjects, the investigator/qualified site staff will record if the subject was rescreened on the rescreening CRF and the original screening number the subject was issued prior to the current screening number.

The date of the new informed consent signature must be entered on the Informed consent CRF to correspond to the new screening subject number. Informed Consent for a rescreened subject must be obtained prior to performing any study-related assessment or collecting any data for the Screening Visit. For rescreening, all screening assessments must be performed as per protocol, except for the tuberculosis (TB) work up, if applicable, if performed not more than 12 weeks before randomization.

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.

During the treatment periods, subjects may be seen at an unscheduled visit, e.g., if they experience deterioration of psoriasis, or AEs that in the opinion of the investigator need intervention or repeated laboratory testing.

Subjects who discontinue study treatment will continue to be followed for safety assessments. They are not considered withdrawn from the study.

Subjects who discontinue study treatment before completing the study, and those who prematurely withdraw from the study for any reason should be scheduled for a study visit 4 weeks after their last study treatment administration, at which time all the assessments listed for EOT 1 (Week 16)/EOT 2 (Week 52) will be performed. Then, subjects should return to the study site for further assessments as indicated under the follow-up visits (F4 and F8).

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

At a minimum, subjects who pre-maturely discontinue the treatment will be contacted for safety evaluations during the 12 weeks following the last dose of study treatment, including final contact at the 12 week point. Documentation of attempts to contact the subject should be recorded in the subject record.

Suggested order of assessments:

Suggested guidelines for conduct of the visit assessments are listed below.

- [redacted]
- Investigator to complete efficacy assessments:
  1. IGA
  2. PASI

  The PASI Score and Investigator's Global Assessment eCRFs must be completed prior to contacting IRT for randomization. At Randomization, the investigator must confirm subject meets IGA mod 2011, PASI and BSA eligibility before randomizing the subject. [redacted]
- All remaining study procedures (e.g. laboratory sample collection, vital signs measurements, ECG, etc.) must be completed prior to study treatment dosing
- Contact IRT to register the subject visit, as applicable.
- Administration of study treatment, as applicable.

Table 6-1 Assessment schedule

Periods	Screen	Treatment Period 1								Treatment Period 2						Unscheduled visit (a)	Post Treatment Follow- up Period	
Week (relative to randomization (R))	≥-4 to ≤-1	R	1	2	3	4	8	12	16 EOT1	20	24	28	32	40	52 EOT2		F4 56	F8 60
Day Assessment	≥-28 to ≤-7	1	8	15	22	29	57	85	113	141	169	197	225	281	365		393	421
Site visit	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Obtain informed consent	X																	
Demographics	X																	
Inclusion/exclusion criteria	X	X																
Smoking history	X																	
Psoriasis medical history / previous psoriasis therapies	X																	
Other medical history and prior medications	X																	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	S	S	S			S			S				S		S	S	S	
Height	X																	
Weight	X	X							X				X		X	X		
Vital signs (blood pressure and pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

R= Randomization; X = assessment to be recorded on clinical database; S = assessment to be recorded on source documentation.

(a) Unscheduled visit: The assessment(s) performed at an unscheduled visit are at the investigator's discretion.

[redacted]

Periods	Screen	Treatment Period 1								Treatment Period 2						Unscheduled visit (a)	Post Treatment Follow- up Period	
Week (relative to randomization (R))	≥-4 to ≤-1	R	1	2	3	4	8	12	16 EOT1	20	24	28	32	40	52 EOT2		F4 56	F8 60
Day Assessment	≥-28 to ≤-7	1	8	15	22	29	57	85	113	141	169	197	225	281	365		393	421
Laboratory sampling: safety panel (Clinical chemistry, hematology)	X	X		X		X	X	X	X	X	X		X		X	X	X	X
Fasting labs: glucose, lipid panel)		X							X		X		X			**X**		
QuantiFERON® TB-Gold In-tube test	X														X	X		
Serum pregnancy test (WoCBP only)	X																	
Urine pregnancy test (local) (WoCBP only)		S							S				S	S	S	S	S	S
Urinalysis (local)	X															X		
[redacted]																		

TB: tuberculosis; X = assessment to be recorded on clinical database; S = assessment to be recorded on source documentation; WoCBP = women of child bearing potential
(a) Unscheduled visit: The assessment(s) performed at an unscheduled visit are at the investigator's discretion.

[redacted]

Periods	**Screen**	**Treatment Period 1**								**Treatment Period 2**						**Unscheduled visit (a)**	**Post Treatment Follow- up Period**	
Week (relative to randomization (R))	**≥-4 to ≤-1**	**R**	**1**	**2**	**3**	**4**	**8**	**12**	**16 EOT1**	**20**	**24**	**28**	**32**	**40**	**52 EOT2**		**F4 56**	**F8 60**
Day Assessment	**≥-28 to ≤-7**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**281**	**365**		**393**	**421**
ECG (standard 12-lead)	X										X				X	X		
Chest X-ray (optional)	S																	
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IGA mod 2011	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																		
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT		S	S	S	S	S	S	S	S	S	S	S	S	S	S			
Administer study treatment during visit		X	X	X	X	X	X	X	X	X	X	X	X	X				
Review home administration diary (c)							S	S	S	S	S	S	S	S	S	S		
Study Completion Form	X																	

ECG: electrocardiogram; eCRF; PASI: Psoriasis Area and Severity Index; IGA: Investigator's Global Assessment; [redacted]; AE: adverse event; IRT: interactive response technology;

X = assessment to be recorded on clinical database; S = assessment to be recorded on source documentation

(a) Unscheduled visit: The assessment(s) performed at an unscheduled visit are at the investigator's discretion.

(c) The following time points are planned for home administrations of study medication: Weeks 6, 10, 14, 18, 22, 26, 30, 34, 36, 38, 42, 44, 46 and 48.

6.1 Information to be collected on screening failures

Subjects who sign the informed consent form and discontinue prior to randomization at Visit 2 (Baseline) are considered screening failures.

For each subject who has signed informed consent and discontinued before entering the double-blind treatment period, IRT must be notified within 5 days and the reason for not being randomized will be entered on the disposition CRF. In addition, the Screening visit date, the Demography CRF, Informed Consent CRF, Inclusion/Exclusion Criteria CRF and Subject rescreening CRF must be completed for rescreened subjects.

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

6.2 Patient demographics/other baseline characteristics

6.2.1 Demographics

Subject demographic data will include: age, sex, race and ethnicity.

6.2.2 Psoriasis medical history / previous psoriasis therapies

The following information should be collected and entered in the CRF capturing Psoriasis history in addition to pre-psoriasis therapies:

- The date of first diagnosis of plaque-type psoriasis (by a physician).
- The previous treatments of psoriasis (including previous use of biologic therapies, as well as phototherapy and/or photo-chemotherapy) and the reason for discontinuation.

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.

6.2.4 Co-morbidities – cardiovascular medical history

Any information pertaining to cardiovascular medical history assessed prior to randomization.

6.2.5 Relevant medical history/current medical conditions

Relevant medical history and current medical conditions present before signing the informed consent should be recorded in the CRF capturing medical history.

Relevant medical history/current medical condition data includes data up to 6 months prior to signing of the informed consent and until the start of study treatment. Whenever possible, diagnoses and not symptoms should be recorded.

Any information pertaining to psoriasis or cardiovascular medical history assessed prior to randomization should be reported.

Chest X-ray (optional)

Chest X-ray is an optional assessment which can be performed during screening at the discretion of the investigator, if warranted for the subjects. This is aimed to detect ongoing infection and particularly tuberculosis or malignancy.

A chest X-ray (or chest MRI at pre specified sites) must only be done after it is fairly certain that the subject meets the inclusion/exclusion criteria, in order to minimize unnecessary exposure to X-ray radiation for subjects.

If the chest X-ray, CT scan, or MRI evaluated by a qualified physician reveals an evidence of untreated infections or malignancies the subject will not be enrolled into the study.

6.2.6 Determination of the tuberculosis status

Determination of the tuberculosis (TB) status will be required before administration of study treatment and should be performed as defined by local guidelines. The TB status must be determined by medical history, signs, symptoms, TB testing (QuantiFERON-TB Gold assay). Any significant findings should be recorded in the TB assessment eCRF and the CRF capturing medical history, as deemed necessary.

QuantiFERON® TB-Gold In-Tube assay

A QuantiFERON® TB-Gold In-Tube assay (QFT) to screen a population for latent tuberculosis infection (Doherty et al 2008) will be used at screening to evaluate the subjects' eligibility for the study. This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin vaccination or by exposure to other Mycobacteria species. Furthermore, this test, in contrast to the purified protein derivative (PPD) skin test, is also insensitive to a booster effect since the subject is not exposed to the vaccine. The assay measures the production of interferon-gamma and presents it relative to a negative and a positive control sample (Manuel and Kumar, 2008). The QuantiFERON®-TB Gold assay test will be supplied by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the study-specific laboratory manual.

The workflow of sample handling in case of positive or indeterminate test results is provided in Figure 6-1.

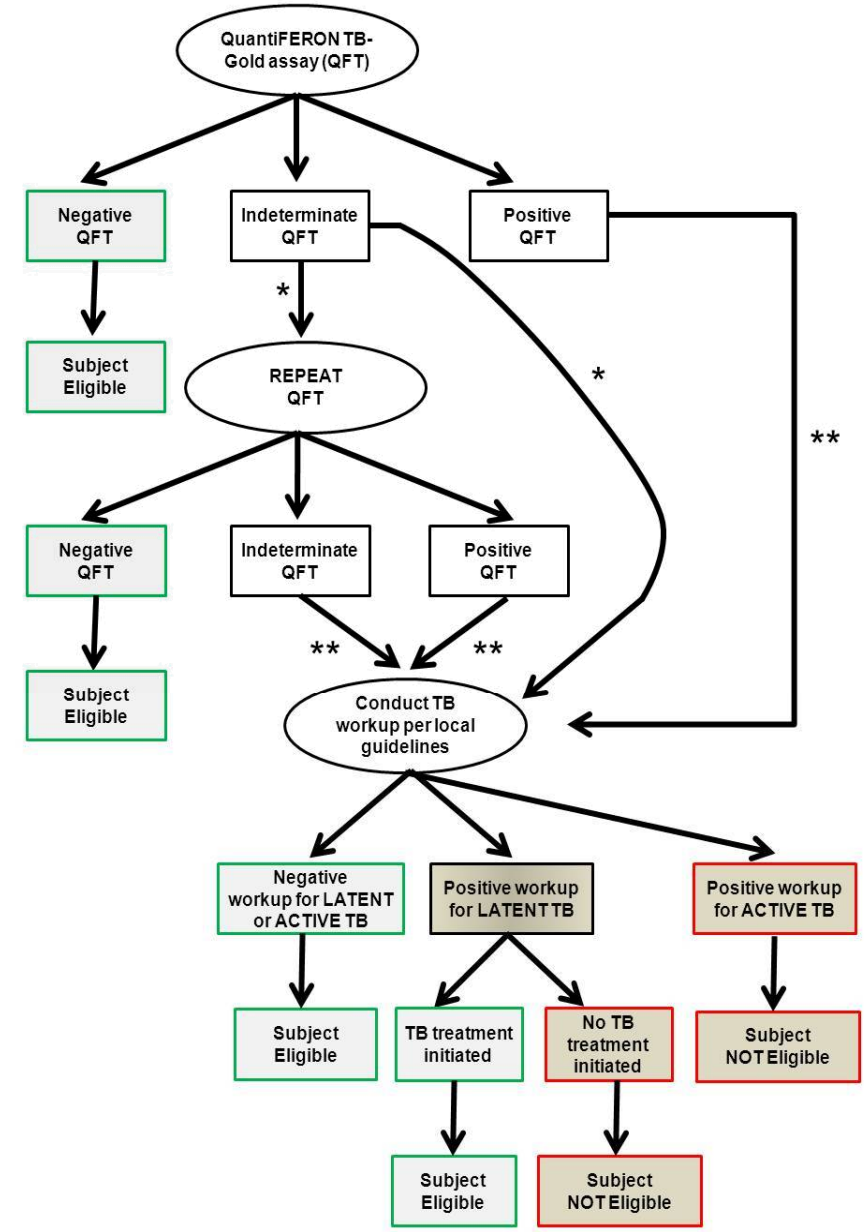
- If the test result is **negative**, the subject may be randomized.
- If the test result is **positive**, the investigator should perform workup for the test result as per local procedures. If a TB workup was conducted prior to the screening the subject, results of the workup can be used to assess eligibility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

Note: 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**, the investigator **may repeat the test once or may proceed directly to perform workup** for the test result as per local procedures. This action is at the discretion of the investigator. If a TB workup was conducted prior to the screening the subject, results of 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**, the investigator should perform workup as per local guidelines. Subjects that test 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 per workup (no signs of latent or active TB) may be randomized to the trial.
    - If the second test is again **indeterminate**, the investigator should perform follow-up for the test result as per local procedures. Subjects tested positive for **latent** TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice. Subjects positive for **active** TB per workup are not eligible for the study. Subjects negative for TB per workup (no signs of latent or active TB) may be randomized to the trial if the workup was conducted within 12 weeks prior to randomization.

Note: if eligibility is being assessed with only 1 test result and a TB workup (i.e., no second TB test will be performed), the TB test to assess eligibility must have been done via the central laboratory for the study within the screening period (within 4 weeks prior to randomization) and TB workup will only be considered if it was completed **within 12 weeks** prior to randomization. Subjects that test 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 per workup (no signs of latent or active TB) may be randomized to the trial

Figure 6-1 Tuberculosis screening flowchart



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

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

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

6.2.7 Other baseline characteristics

Baseline characteristic data to be collected on those indicated with an "X" in Table 6-1 for the screening and randomization visit.

6.3 Treatment exposure and compliance

All doses of study treatment administration will be recorded on the appropriate CRF. Compliance to the planned administration schedule is expected to be high since most of the administrations of study treatment will be done in the presence of the investigator or study personnel. Compliance will also be assessed by means of site and subject-specific drug accountability by Novartis study personnel during the site monitoring visits using medication pack numbers, Drug Label Form information and information collected by IRT.

6.4 Efficacy

The following order should be applied when performing the efficacy assessments at study visits:

- Investigator's Global Assessment for general psoriasis (IGA mod 2011; scale from 0-4)
- Psoriasis Area and Severity Index (PASI; score from 0 – 72)
- [redacted]

6.4.1 Investigator Global Assessment (IGA mod 2011)

IGA mod 2011 will be conducted for overall psoriatic disease as indicated in Table 6-2. It is recommended that the same evaluator conduct the assessment throughout the study whenever possible.

In collaboration with health authorities, in particular the FDA, the IGA mod 2011 scale (see Table 6-2) has been developed based on a previous version of the scale used in secukinumab Phase 2 studies. The only change from the Phase 2 scale to Phase 3 scale was to condense the very severe and severe subjects into one category "severe". The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between them.

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 CRF.

Table 6-2 The 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	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling.
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling.
4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe / coarse scaling covering almost all or all lesions.

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

Based on this scale, a subject will be eligible to participate in the study if the subject has an IGA mod 2011 score at baseline (Visit 2) of 3 or 4.

Based on this scale, a subject will be considered as IGA mod 2011 0 or 1 responder if the subject achieves a score of 0 or 1 and improved by at least 2 points on the IGA scale compared to baseline.

6.4.2 Assessment of total Body surface Area and Psoriasis Area Severity Index

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

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for PASI assessment). The following calculations will be done: 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 4 percentages will be added up to estimate the total BSA affected by plaque-type psoriasis. The PASI scoring system is further described in Table 6-3.

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 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. Further 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.

When scoring the severity of erythema, scales should not be removed.

Table 6-3 The 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 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 6=90-100%
Trunk (T)‡	0=none 1=slight 2=moderate 3=severe	0=none 1=slight 2=moderate 3=severe	0=none 1=slight 2=moderate 3=severe	0=no involvement 1=>0-<10% 2=10-<30%

	4=very severe	4=very severe	4=very severe	3=30-<50% 4=50-<70% 5=70-<90% 6=90-100%
Upper limbs (U)	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 6=90-100%
Lower limbs (L)§	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 6=90-100%

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

† 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.

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 using the 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 6-3.

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

A subject will be considered as a PASI 90 responder if s/he achieves a reduction of 90% or more of the PASI score, compared to baseline, at a given time point.

[redacted]

During the study, at each visit, the PASI score will be calculated and response will be classified according to the definitions from Committee for Medicinal Products for Human Use (CHMP) guidelines for psoriasis CHMP/EWP/2454/ 02 2004.

[redacted]

- **PASI 90 response:** subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline

[redacted]

In addition to the assessment of PASI, the investigator will assess whether new pustular psoriasis, or new erythrodermic psoriasis, or more inflammatory psoriasis occurred (yes/no).

[redacted]

6.4.4 Appropriateness of efficacy assessments

The PASI score, the assessment of the severity of the psoriasis symptoms and the extent to which the subject's body area is affected by the disease, is considered acceptable by health authorities (CHMP/EWP/2454/02 2004) to assess efficacy in conjunction with Investigator's Global Assessment mod 2011 (IGA mod 2011).

6.5 Safety

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

- Evaluation of all AEs and SAEs including injection site hypersensitivity reactions, vital signs, laboratory assessments and occurrence of infections.
- Physical examination
- Vital signs
- Height and weight
- Laboratory evaluations (Hematology, Clinical chemistry, Urinalysis)
- ECG
- Pregnancy and assessments of fertility

[redacted]

6.5.1 Physical examination

A physical examination, including general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems will be performed as indicated in Table 6-1.

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

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

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of the study, i.e. all findings prior to signing the informed consent form (ICF), must be included in the CRF capturing Medical History. Significant findings after enrollment into the study that meets the definition of an adverse event must be recorded on the CRF capturing Adverse Event.

6.5.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed at every scheduled visit as indicated in Table 6-1. Whenever possible, assessments should be performed by the same study site staff member throughout the study.

After the subject has been sitting for about five minutes, with back supported and both feet placed on the floor, systolic and diastolic **blood pressure will be measured twice** and will be recorded in the source documentation (measurements separated by 1 to 2 minutes) using a validated device, with an appropriately sized cuff (Mancia et al 2007). In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. The average of the two measurements will be entered on the CRF capturing Vital Signs.

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

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

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

6.5.3 Height and weight

Height and body weight will be measured as listed in Table 6-1.

Height and body weight will be measured in indoor clothing, but without shoes. Whenever, possible, body weight assessments should be performed by the same study site staff member; the same scale should be used throughout the study.

6.5.4 Laboratory evaluations

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

Subjects should avoid smoking within the hour preceding the blood draws.

Appendix 1 shows the extended laboratory ranges that are considered clinically notable.

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

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count will be measured at all scheduled study visits, within the visit window suggested in Table 6-1.

6.5.4.2 Clinical chemistry

Serum chemistry will include urea, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), Gamma-Glutamyl Transferase (GGT), alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, amylase, lipase and uric acid. Serum chemistry will be measured at all scheduled study visits within the visit window specified in Table 6-1.

6.5.4.3 Fasting Laboratory evaluations

Fasting (8 hour duration with water *ad libitum*) laboratory evaluations will be assessed as at baseline as indicated in Table 6-1.

6.5.4.3.1 Plasma glucose

Fasting plasma glucose will be taken as a fasting blood sample as indicated in Table 6-1.

6.5.4.3.2 Lipid panel

A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), cholesterol, triglycerides, lipoprotein (a), apolipoprotein B, apolipoprotein A-1, and adiponectin will be measured from a fasting blood sample as indicated in Table 6-1.

6.5.4.4 Urinalysis

Dipsticks will be provided to the study sites for local urinalysis assessments. The sites will record the results in the appropriate CRF for each subject. Standard dipstick measurements for specific gravity, protein, glucose, pH, blood, urine blood dipstick (non-hemolyzed), urine blood dipstick (hemolyzed), bilirubin, ketones and WBC will be done as indicated in Table 6-1.

6.5.5 Electrocardiogram (ECG)

A standard single 12-lead ECG will be ECGs will be measured according to the assessment schedule in Table 6-1 and analyzed centrally.

Each ECG tracing should be labeled with study number, subject number, date and time, and filed in the study site source documents. ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings at screening must be discussed with the sponsor before administration with investigational treatment.

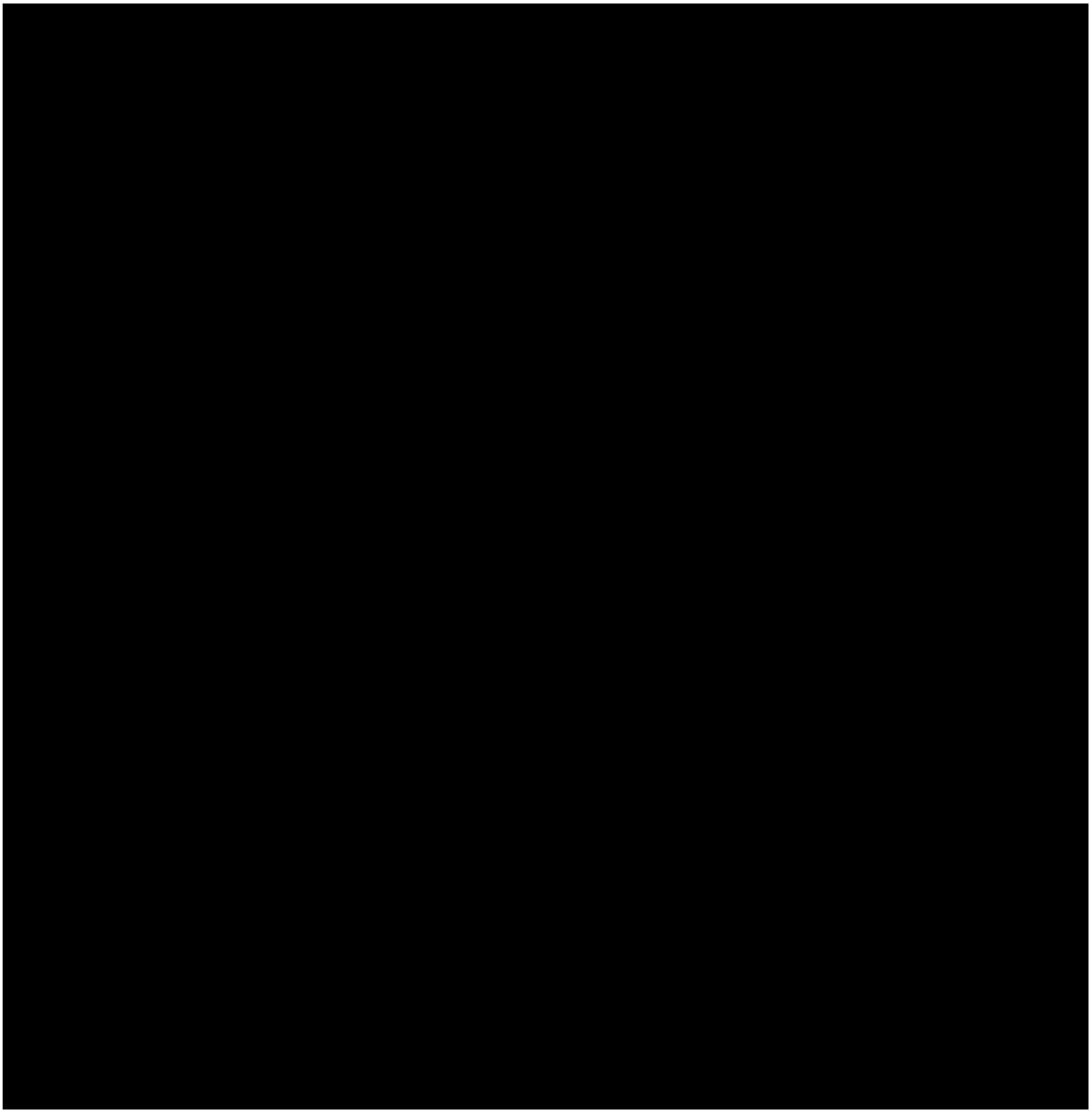
Although there is no exclusion criterion based on ECG results, the ECG at the screening visit must be reviewed for major abnormalities prior to dosing.

Clinically significant abnormalities should be recorded on the relevant section of the CRF capturing medical history/ Current medical conditions/AE as appropriate.

6.5.6 Pregnancy and assessments of fertility

Pregnancy tests will be performed in all women of child-bearing potential (see Section 4.2 for definition of child-bearing potential), as indicated in Table 6-1. Additional pregnancy testing might be performed if requested by local requirements.

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



7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the

study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subject with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

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

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment (suspected: Yes / No)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding study treatment

  All adverse events must be treated appropriately. Treatment may include one or more of the following:
  - no action taken (e.g. further observation only)
  - study treatment dosage increased/reduced
  - study treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- subject hospitalized/subject's hospitalization prolonged (see Section 7.2 for definition of SAE)

- its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

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

Worsening of psoriasis in this study is evaluated via the use of PASI, IGA mod 2011 and [redacted] is not expected to be captured as an AE in the CRF capturing adverse events. Exceptions include cases when a) a new type of psoriasis is diagnosed e.g. guttate psoriasis or b) the worsening of psoriasis is so severe that a qualitatively different status is reached.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the subject.

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

  - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. 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 it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the 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 (please refer to Annex IV, ICH-E2D Guideline).

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

7.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 12 weeks following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after 12 week period following the last administration of study treatment should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

All SAEs reported up to the subject's last visit will be reported in the appropriate eCRF. SAEs beyond the last visit will only be recorded in the Novartis Drug Safety and Epidemiology database.

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

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring should be entered into the appropriate CRFs.

Please refer to Table 13-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 13-1 in Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 13-2 in Appendix 2.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the subject. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the appropriate CRFs.

- If the elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the subject if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRFs.

7.4 Reporting of study treatment errors including misuse/abuse

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

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

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

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

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

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

7.5 Pregnancy reporting

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

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy

follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

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

8 Data review and database management

8.1 Site monitoring

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

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

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

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 secure web-enabled software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that

the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

8.3 Database management and quality control

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

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

ECGs will be analyzed centrally and results will be sent electronically to Novartis (or a designated CRO). Any clinically significant findings will be reported as (cardiovascular) medical history or AE depending upon timing of ECG assessment compared to screening.

[redacted]

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

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

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

The following analysis sets will be used in this trial:

Randomized set: The randomized set will be defined as all subjects who were randomized. Unless otherwise specified, mis-randomized subjects (mis-randomized in IRT) will be excluded from the randomized set.

Full analysis set (FAS): The FAS will be comprised of all subjects from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization.

Safety set (SAF): The safety set includes all subjects who took at least one dose of study treatment during the treatment period. Subjects will be analyzed according to treatment received.

9.2 Patient demographics and other baseline characteristics

Demographics and baseline characteristics

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

Medical history

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

9.3 Treatments

Study treatments

The analysis of study treatment data will be based on the safety set.

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

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

Prior and concomitant treatments

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

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

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

Psoriasis specific prior treatments will be presented as well including number of prior systemic and biologic psoriasis therapies as well as reason for discontinuation.

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

9.4 Analysis of the primary variable(s)

This section will detail the statistical analysis of the primary endpoint. Details of the hypothesis testing strategy including primary and secondary endpoints to handle multiplicity are provided in Section 9.5.1.

9.4.1 Primary Variable(s)

The primary efficacy variable is PASI 90 response at Week 16. The analysis of primary variable will be based on the FAS.

9.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypothesis for PASI 90 response at Week 16 being tested is that secukinumab 300 mg every 2 weeks is not superior in the proportion of subjects with PASI 90 response at Week 16 versus secukinumab 300 mg every 4 weeks.

[redacted]

The following hypotheses will be tested

H_1: $p_1 - p_0 \leq 0$ versus H_{A1}: $p_1 - p_0 > 0$,

In other words:

H_1: secukinumab 300 mg every 2 weeks is not superior to secukinumab 300 mg every 4 weeks with respect to PASI 90 response at Week 16.

The primary analysis method will be the logistic regression model with treatment group and baseline weight, baseline PASI score as explanatory variables. Odds ratio will be computed for the comparison of secukinumab 300 mg every 2 weeks versus secukinumab 300 mg every 4 weeks utilizing the logistical regression model fitted. In case of non-convergence, Fisher's exact test will be applied. Confidence intervals for risk difference will be provided.

The hypotheses H_1 will be tested at level 2.5% (one-sided).

9.4.3 Handling of missing values/censoring/discontinuations

Response variables based on PASI score and IGA mod 2011 score will be imputed with multiple imputation (MI) as primary imputation method for the missing values. Multiple imputation (MI) is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Within this analysis the PASI score or IGA mod 2011 categories will be imputed and response variables will be derived based on the imputed scores. In the multiple imputation analysis the response status will be imputed based on the individual treatment arm information.

9.4.4 Sensitivity analyses

Primary variable and key secondary variable will be evaluated using logistic regression as described in primary analysis method with modified non-responder imputation.

Missing values with respect to response variables based on PASI score and IGA mod 2011 score will be imputed with non-response regardless of the reason for missing data (e.g., premature study discontinuation, missed visit, administrative issues), with the exception of the followings:

- If a subject dropped out the study prior to last scheduled visit and being responder consecutively at least for two preceding visits, the subject will be imputed as responder for the last scheduled visit.
- If a subject who was responder at visit x-1 and visit x+1 but has missing data at visit x, then the subject will be imputed as responder for visit x, except for the missing data at last visit in the treatment period.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

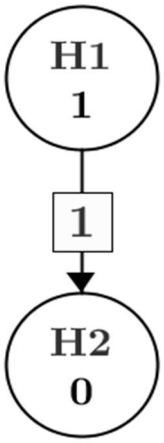
The secondary variable in testing strategy is the IGA mod 2011 0 or 1 response at Week 16 (for superiority comparison of secukinumab 300 mg every 2 weeks versus secukinumab 300 mg every 4 weeks). The IGA mod 2011 0 or 1 response at Week 16 will be analyzed analogously to PASI 90 response at Week 16 (i.e., logistic regression analysis).

The analysis of secondary variable will be based on FAS.

H_2: secukinumab 300 mg every 2 weeks is not superior to secukinumab 300 mg every 4 weeks with respect to IGA mod 2011 0 or 1 response at Week 16.

Testing strategy

The family-wise type-I-error will be set to α=2.5% (one-sided). The graphical approach of Bretz (Bretz et al 2009) for sequentially rejective testing procedures is used to illustrate the hierarchical testing strategy.



One-sided p-values will be derived. Each hypothesis is tested sequentially at α=2.5% (one-sided). The testing sequence will continue to H_2 at α (one-sided) only if H_1 has been rejected.

9.5.2 Safety variables

All safety evaluations will be performed on the Safety set.

Adverse events

Treatment-emergent adverse events will be summarized. Only primary paths within MedDRA will be considered for adverse event reporting. The definition for "treatment-emergent" is as follows:

- Events started after the first dose of study medication or events present prior to the first dose of study medication but increased in severity based on preferred term
- Started prior to the last dose plus 84 days (inclusive)

AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects having at least one AE, having an AE in each primary system organ class and having each individual AE (preferred term).

Summaries will also be presented for AEs by severity and for study treatment related AEs. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

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

Separate summaries will be provided for death, serious adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment (including study treatment discontinuation).

Exposure adjusted incidence rates will be provided for selected adverse events.

Laboratory data

The summary of laboratory evaluation will be presented for three groups of laboratory tests (hematology, serum chemistry and urinalysis). Descriptive summary statistics for the change from baseline to each study visit will be presented by laboratory test group, laboratory tests (i.e., lab parameters) and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline.

For each lab parameter, the maximum change (maximum decrease and maximum increase) from baseline will be analyzed analogously.

In addition, shift tables will be provided for all lab parameters to compare a subject's baseline laboratory evaluation relative to the most extreme post-baseline laboratory test value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low or high. These summaries will be presented by laboratory test and treatment group.

[redacted]

Vital signs

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

ECG

Summary statistics will be presented for ECG variables by visit and treatment group.

[redacted]

9.7 Interim Analyses

A primary endpoint analysis (PEA) may be conducted when all subjects have completed the Week 16 visit at which the primary endpoint is assessed. Additional analyses may be performed to support health authority interactions as necessary.

9.8 Sample size calculation

The sample size has been calculated to detect a clinical relevant treatment difference (i.e. 15%) between secukinumab 300 mg every two weeks and secukinumab 300 mg every four weeks. Based on this, the total sample size is approximately 330 subjects, with body weight ≥ 90 kg at randomization. i.e., 165 subjects will be randomized to each dose regimen (300 g every 2 weeks and 300 mg every 4 weeks) using a balanced randomization.

Secukinumab 300 mg every two weeks will be tested versus secukinumab 300 mg every four weeks with respect to the primary endpoint PASI 90 response at Week 16, and sequentially the secondary endpoint IGA mod 2011 0 or 1 at Week 16. The family-wise type-I-error will be 2.5% (one-sided)

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible 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 applicable 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 must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the 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 must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, 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.

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

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

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

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal Standard Operating Procedures (SOPs), and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to 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 must be followed.

12 References

References are available upon request.

Bretz F, Maurer W, Brannath W, et al (2009) A graphical approach to sequentially rejective multiple test procedures. Statist. Med; 28:586-604.

Chobanian AV, Bakris GL, Black HR, et al (2003) Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension; 42:1206-1252.

Committee for medicinal products for human use (CHMP), European Medicines Agency for the Evaluation of Medicines for Human Use (2004) Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. CHMP/EWP/2454/02 corr document. London, UK.

Doherty SD, Van Voorhees A, Lebwohl MG, et al (2008) National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. J Am Acad Dermatol; 59(2):209-217.

[redacted]

Fredriksson T, Pettersson U (1978) Severe Psoriasis – Oral Therapy with a New Retinoid. Dermatologica; 157:238-244.

Gottlieb AB, Griffiths CEM, Ho VC, et al (2005) Oral pimecrolimus in the treatment of moderate to severe chronic plaque-type psoriasis: a double –blind, multicenter, randomized, dose-finding trial. British Journal of Dermatology; 152:1219-1227.

Kimball AB, Wu EQ, Guerin A, et al (2012) Risk of developing psychiatric disorders in pediatric patients with psoriasis. J Am Acad Dermatol; 67 (4):651-7.

Langley RG, Elewski BE, Lebwohl M, et al (2014) Secukinumab in Plaque Psoriasis-Results of Two Phase 3 Trials. N ENGL J MED; 371 (4): 326-338.

Mancia G, De Backer G, Dominiczak A, et al (2007) 2007 Guidelines for the Management of Arterial Hypertension. Journal of Hypertension; 25:1105-1187.

Manuel O, Kumar D (2008) QuantiFERON-TB Gold assay for the diagnosis of latent tuberculosis infection. Expert rev. Mol. Diagn; 8(3):247-255.

Newcombe RG (1998) Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in Medicine; 17:857-872.

Papp KA (2006) The long-term efficacy and safety of new biological therapies for psoriasis. Arch Dermatol Res; 298:7-15.

Papp KA, Langley RG, Lebwohl M, et al (2008) Efficacy and Safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet; 371:1675-84.

Thaci D, Blauvelt A, Reich K, et al (2015) Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am ACAD Dermatol; 73 (3):400-409.

van Lümig PPM, Lecluse LLA, Driessen RJB, et al (2010) Switching from etanercept to adalimumab is effective and safe: results in 30 patients with psoriasis with primary failure, secondary failure or intolerance to etanercept. British Journal of Dermatology; 163:838-846.

Weisman S, Pollack CR, Gottschalk RW (2003) Psoriasis disease severity measures: comparing efficacy of treatments for severe psoriasis. Journal of Dermatological Treatment; 14:158-165.

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.

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

Liver Function and Related Variables

- Alanine transaminase (ALT) (SGPT): > 3 x Upper Limit of Normal (ULN)
- Aspartate transaminase (AST) (SGOT): > 3 x ULN
- Total bilirubin: > 2 x ULN
- Alkaline phosphatase: > 2.5 x ULN

Hematology Variables

- Hemoglobin: ≥ 20 g/dL decrease from baseline
- Platelet count: < Lower Limit of Normal (LLN)
- White blood cell count: < 0.8 x LLN
- Neutrophils: < 0.9 x LLN
- Eosinophils: > 1.1 x ULN
- Lymphocytes: > 1.1 x ULN

13.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 13-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal; INR: international normalized ratio

Table 13-2 Follow-up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete appropriate CRF to record the AE and any contributory factors	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete appropriate CRF to record the AE and any contributory factors	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete appropriate CRF to record the AE and any contributory factors	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• Establish causality • Complete appropriate CRF to record the AE and any contributory factors	
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete appropriate CRF to record the AE and any contributory factors	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete appropriate CRF to record the AE and any contributory factors	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete appropriate CRF to record the AE and any contributory factors	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete appropriate CRF to record the AE and any contributory factors	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete appropriate CRF to record the AE and any contributory factors	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.