

Global Clinical Development - General Medicine

Secukinumab (AIN457)

Clinical Trial Protocol [CAIN457A2326] / NCT02826603

A 52-week, multicenter, randomized, double-blind study of secukinumab (300 mg) to demonstrate efficacy as assessed by Psoriasis Area and Severity Index and Investigator's Global Assessment after 12 weeks of treatment, compared to ustekinumab, and to assess long-term safety, tolerability, and efficacy in subjects with moderate to severe plaque psoriasis (CLARITY)

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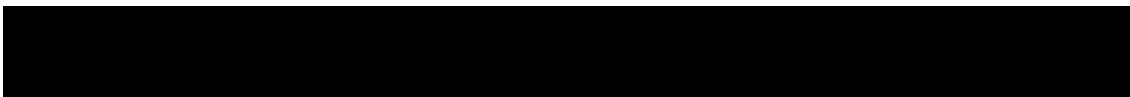
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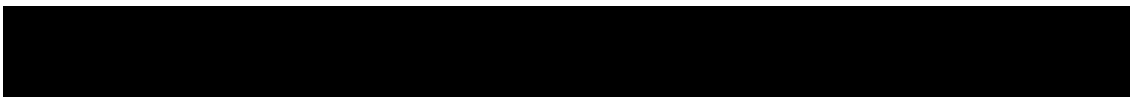
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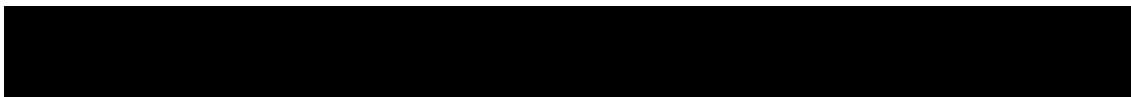
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List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
Bpm	Beats per minute
BSA	Body Surface Area
CFR	US Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Terminology Criteria
DB	Database
	
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment (epoch)
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions For Use
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011
IL	Interleukin
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LFT	Liver function test
MedDRA	Medical dictionary for regulatory activities
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	once a day
PASI	Psoriasis Area and Severity Index



SAE	Serious Adverse Event
s.c.	subcutaneous, subcutaneously
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TCS	Topical corticosteroid
TNF	Tumor necrosis factor
UV	Ultraviolet
WBC	White blood cells
WHO	World Health Organization

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 subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
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
Subject ID	A unique number assigned to each subject upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
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 (TD)	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 consent (WoC)	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

Amendment 1

Amendment rationale

Per the new protocol, all drug administrations will be performed at the site in order to minimize potential influence of subjects' non-compliance at home administrations in this head to head study.

Also, the Non-responder imputation method is updated. This change is in line with [REDACTED] recommendations to impute subjects with all post-baseline missing values as non-responders according to the Intent-to-treat (ITT) principle.

At the time of amendment release, the study has not yet enrolled any subjects.

Changes to the protocol

The major changes are listed below:

- All home visits (study treatment administrations at home) are converted to site visits (study treatment administrations at site).
- Non-responder imputation method is updated.
- Sensitivity analysis will also be performed on key secondary objectives.

These changes were implemented throughout the relevant sections of the protocol.

This protocol amendment also includes the correction of typographical and formatting errors and editorial changes for increased clarity of the text.

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

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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



Protocol summary

Protocol number	CAIN457A2326
Title	A 52-week, multicenter, randomized, double-blind study of secukinumab (300 mg) to demonstrate efficacy as assessed by Psoriasis Area and Severity Index and Investigator's Global Assessment after 12 weeks of treatment, compared to ustekinumab, and to assess long-term safety, tolerability, and efficacy in subjects with moderate to severe plaque psoriasis (CLARITY)
Brief title	Study of efficacy and safety of secukinumab compared to ustekinumab in subjects with plaque psoriasis
Sponsor and Clinical Phase	Novartis 3b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to confirm the superiority of secukinumab versus ustekinumab (weight based dosing, according to approved labelling) based on PASI 90 and IGA mod 2011 0/1 response rates at Week 12 in treatment of moderate to severe plaque psoriasis.
Primary Objective(s)	The primary objective of this study is to demonstrate the superiority of secukinumab 300 mg compared to ustekinumab in subjects with moderate to severe plaque psoriasis with respect to both PASI 90 and IGA mod 2011 0/1 response at Week 12. Moreover, this study will assess the long-term efficacy, safety and tolerability of secukinumab versus ustekinumab over a period of 52 weeks.
Secondary Objectives	The key secondary objectives of the study are to demonstrate the superiority of secukinumab compared to ustekinumab with respect to: <ul style="list-style-type: none"> • PASI 75 response at Week 12 • PASI 75 response at Week 4 • PASI 90 at Week 16 • PASI 100 at Week 16 • IGA mod 2011 0/1 at Week 16 • PASI 100 at Week 12 • PASI 75 at Week 16 • PASI 90 at Week 52
Study design	This is a multicenter, randomized, double-blind, active-controlled, parallel-group trial in approximately 1100 subjects with moderate to severe chronic plaque-type psoriasis. It is expected that subjects will be enrolled at approximately 200-250 study sites worldwide. The study consists of 3 epochs: screening (of at least 2 weeks and up to 4 weeks), treatment epoch (of 52 weeks: from randomization to Week 52), and follow-up epoch (of 8 weeks: visits F4 and F8 to be conducted at 8 and 12 weeks after last study treatment, for subjects with premature treatment discontinuation only).
Population	This study will randomize approximately 1100 male and female subjects aged ≥18 years.
Key Inclusion criteria	1. Subjects must give a written, signed and dated informed consent

	<ol style="list-style-type: none"> 2. Men or women must be at least 18 years of age at the time of screening 3. Chronic plaque-type psoriasis present for at least 6 months before randomization 4. Moderate to severe plaque psoriasis as defined at randomization by: <ul style="list-style-type: none"> • PASI score of ≥ 12 and • Body Surface Area (BSA) affected by plaque-type psoriasis $\geq 10\%$ and • IGA mod 2011 ≥ 3 (based on a scale of 0–4) 5. Candidate for systemic therapy, defined as having psoriasis inadequately controlled by: <ul style="list-style-type: none"> • Topical treatment (including topical corticosteroids) and/or • Phototherapy and/or • Previous systemic therapy
Key Exclusion criteria	<ol style="list-style-type: none"> 1. Forms of psoriasis other than plaque psoriasis 2. Drug-induced psoriasis 3. Ongoing use of prohibited treatments 4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17RA, or ustekinumab, or any therapies targeting IL-12 or IL-23 5. Use of any other investigational drugs within 5 half-lives of the investigational treatment before study drug initiation 6. Pregnant or nursing (lactating) women
Study treatment	<ul style="list-style-type: none"> ○ Investigational treatment <ul style="list-style-type: none"> • Secukinumab 150 mg, 1 ml liquid formulation in a pre-filled syringe ○ Reference treatment <ul style="list-style-type: none"> • Secukinumab placebo, 1 ml liquid formulation in a pre-filled syringe • Ustekinumab 45 mg, 0.5 ml liquid formulation in a pre-filled syringe
Efficacy assessments	<ul style="list-style-type: none"> • IGA mod 2011 • PASI
Key safety assessments	<ul style="list-style-type: none"> • Adverse event monitoring • Physical examinations • Safety laboratory tests
Data analysis	<p>The primary analysis method will be the logistic regression with treatment group; baseline bodyweight strata and baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons of secukinumab dose regimens versus ustekinumab 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.</p>
Key words	<p>Plaque psoriasis, secukinumab, ustekinumab</p>

1 Introduction

1.1 Background

Psoriasis is a chronic relapsing disease of the skin characterized by variable clinical features. The lesions are classified as erythemato-squamous, 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 exclusively on the scalp. Other manifestations of psoriasis are guttate, inverse, erythrodermic, nail and palmoplantar psoriasis.

Extensive clinical experience with TNF α -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 a TNF α -inhibitor. This inadequate response may imply either a primary unsatisfactory response (e.g. not achieving a decrease in Psoriasis Area and Severity Index (PASI) score of at least 50% after adequate duration of treatment), an initially adequate response that is lost over time (secondary failure) or intolerance for the TNF α -inhibitor. The percentage of patients with an inadequate response to TNF α -inhibitors can be as high as 40-60% (Van Lümig et al 2010).

In routine medical practice, given the limited number of therapeutic agents available, it has become common practice to switch medications that are structurally distinct but therapeutically similar to achieve an improved clinical result or to restore a clinical result. Such therapeutic interchange is now being applied to biological agents to treat moderate to severe plaque psoriasis (Vender et al 2011).

Studies have shown that a switch from one TNF α -inhibitor to another TNF α -inhibitor may be successful (Bissonnette et al 2010) although it remains largely unclear as to why such a switch can be effective. Possible explanations are: different mode of action or difference in binding site or binding affinity. Other possible explanations may include neutralizing antibodies directed against the first TNF α -inhibitor.

However, most studies have shown that the response to a second or third TNF α -inhibitor is lower than that observed in patients who are treatment-naïve to TNF α -inhibitors. This phenomenon is most evident in patients who are primary non-responders to initial TNF α -inhibitor (Woolf et al 2010). In addition, an adequate response to the second or third TNF α -inhibitor can sometimes only be obtained or maintained by increasing the dose or the frequency of dose thereby increasing the likelihood of the occurrence of side effects (Haitz and Kalb 2007). Thus, there remains a clinical need for alternative systemic therapies for the treatment of moderate to severe plaque psoriasis that combine robust short- and long-term efficacy with an acceptable safety profile.

The arrival of a new class of systemic, biological drugs such as usteki numab (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 III studies ([Leonardi et al 2008](#); [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](#)).

One study showed good efficacy when patients were switched to ustekinumab after an inadequate primary response to etanercept. However, the ustekinumab response rate was lower in the previously treated etanercept inadequate responders (PASI 90 response rate 23.4%) than in patients naïve for etanercept (44.7%). In addition, clinical response was only achieved with the highest dose of ustekinumab (90 mg) ([Griffiths et al 2010](#)).

A number of IL-17A and IL-17RA inhibitors are being or have been investigated in Phase III studies for the treatment of a range of immune mediated inflammatory diseases, including plaque type psoriasis. With the approval of secukinumab for treatment of moderate-to-severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy, the first treatment option in this class became available for clinicians in major markets such as the United States, European Union, Japan, and Canada.

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 (Cosentyx®) with a recommended dose of 300 mg was approved in 2014 in Japan, in 2015 in the US, in the EU and in Switzerland for the treatment of moderate to severe plaque psoriasis in adults. 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.

The Investigator's Brochure ([IB 2015](#)) provides a more detailed review of the pre-clinical and clinical information on secukinumab.

Secukinumab, which has a different mode of action to TNFα-inhibitors, has proven to be a suitable alternative for consecutive TNFα-inhibitor therapy after inadequate response to the previous TNFα-inhibitor. In two pivotal Phase 3 trials (ERASURE and FIXTURE), secukinumab was associated with a rapid reduction in psoriasis symptoms, elicited significantly greater PASI 75 rates and higher rates of 0 or 1 responses on the modified investigator's global assessment (IGA mod 2011) than placebo at Week 12, and with continued treatment was associated with sustained high response rates in a majority of patients through Week 52. The FIXTURE study showed superior efficacy of secukinumab over the TNF inhibitor etanercept; PASI 75 at Week 12 being 77% with secukinumab 300 mg vs. 44% with etanercept and IGA mod 2011 0/1 being 62% with secukinumab 300 mg vs. 27% with etanercept ([Langley et al 2014](#)). Furthermore, because secukinumab targets a

different interleukin (i.e., IL17A), it has also proved to be an alternative for ustekinumab, either as preferred “switch” drug or as a first line drug in the treatment of moderate to severe plaque psoriasis.

In a recent 52-week, double blind study (CLEAR), secukinumab (79.0%) has proven to be superior to ustekinumab (57.6%) as assessed by PASI 90 response at Week 16 ($p < 0.0001$). The PASI 100 response rate at Week 16 was also significantly greater with secukinumab (44.3%) than ustekinumab (28.4%) ($p < 0.0001$). Thus, the study demonstrated that secukinumab was superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis with a similar safety profile.

1.2 Purpose

The purpose of this study is to confirm the superiority of secukinumab versus ustekinumab (weight based dosing, according to approved labelling) based on PASI 90 and IGA mod 2011 0/1 response rates at Week 12 in treatment of moderate to severe plaque psoriasis.

Moreover, this study will assess the long-term efficacy, safety and tolerability of secukinumab versus ustekinumab over a period of 52 weeks to support the long-term use of secukinumab compared with ustekinumab in subjects suffering from moderate to severe plaque psoriasis.

2 Study objectives and endpoints

2.1 Primary objectives

The co-primary objectives are:

To demonstrate the superiority of secukinumab compared to ustekinumab in subjects with moderate to severe plaque psoriasis with respect to both PASI 90 and IGA mod 2011 0/1 response at Week 12

2.2 Secondary objectives

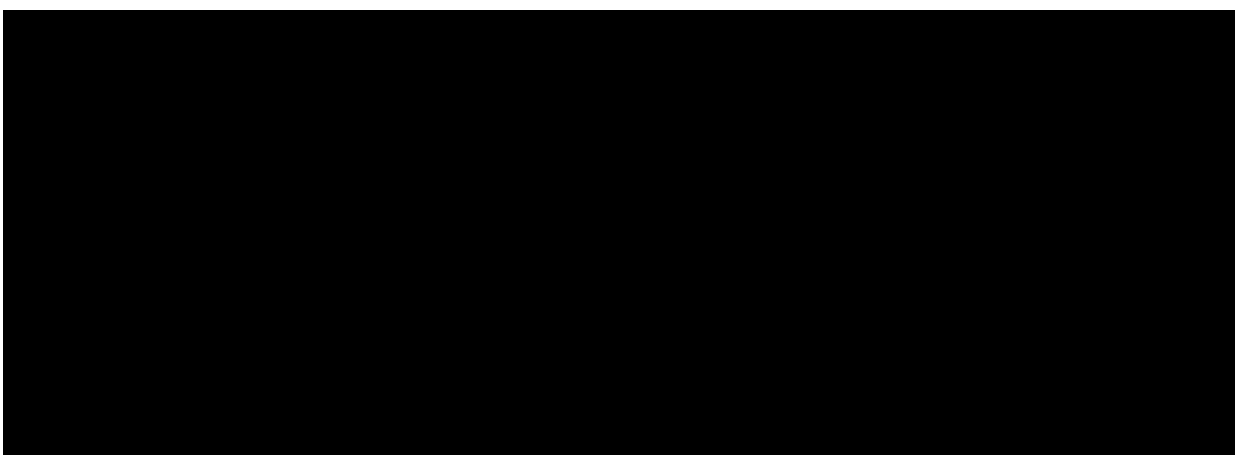
2.2.1 Key secondary objectives

- To demonstrate the superiority of secukinumab compared to ustekinumab in subjects with moderate to severe plaque psoriasis with respect to:
 - PASI 75 response at Week 12
 - PASI 75 response at Week 4
 - PASI 90 at Week 16
 - PASI 100 at Week 16
 - IGA mod 2011 0/1 at Week 16
 - PASI 100 at Week 12

- PASI 75 at Week 16
- PASI 90 at Week 52

2.2.2 Other secondary objectives

To investigate the clinical safety of secukinumab compared to ustekinumab as assessed by adverse event monitoring, vital signs, and clinical laboratory variables.



2.4 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
Primary		
To demonstrate the superiority of secukinumab compared to ustekinumab with respect to both PASI 90 and IGA mod 2011 0/1 response at Week 12	<p>Title: PASI 90 and IGA mod 2011 0/1 after 12 weeks of treatment</p> <p>Unit of Measure: PASI, IGA mod 2011</p> <p>Description: PASI will be assessed/calculated as per usual standard.</p> <p>Investigator will assess severity of disease using a validated scale (IGA mod 2011) and rate the disease from a score of 0 (clear skin) to 4 (severe disease).</p> <p>Time frame: Week 12</p>	Section 9.4
Key Secondary		
To demonstrate the superiority of secukinumab compared to ustekinumab with	<p>Title: PASI 75 after 4, 12 and 16 weeks of treatment PASI 90 after 16 and 52 weeks of treatment</p>	Section 9.5



OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
respect to PASI 75 response at Weeks 4, 12 and 16; PASI 90, PASI 100, IGA mod 2011 0/1 at Week 16; PASI 100 at Week 12; and PASI 90 at Week 52	PASI 100 after 12 and 16 weeks of treatment IGA mod 2011 0/1 after 16 weeks of treatment Unit of Measure: PASI, IGA mod 2011 Description: PASI and IGA mod 2011 0/1 will be assessed at baseline and at regular intervals until Week 52. Time frame: Week 4, Week 12, Week 16, Week 52	
Other Secondary		
To investigate the clinical safety and tolerability of secukinumab 300 mg in comparison to ustekinumab	Endpoint: Clinical safety and tolerability. Unit of Measure: vital signs, clinical laboratory variables, adverse events monitoring Time frame: up to 52 weeks	Section 9.5

3 Investigational plan

3.1 Study design

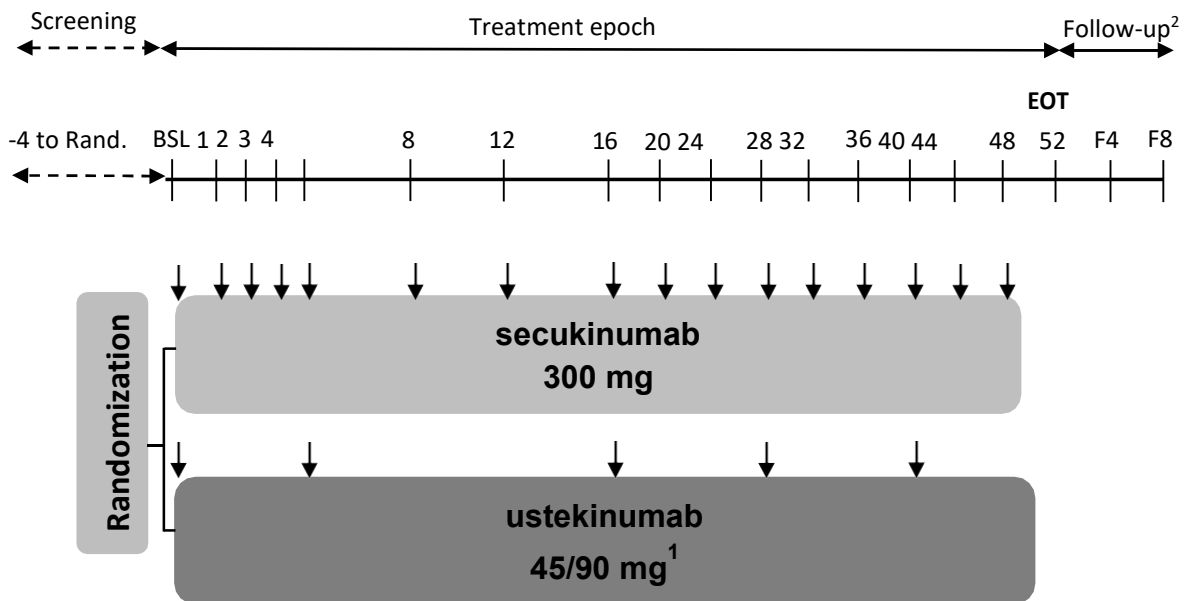
This is a multicenter, randomized, double-blind, active-controlled, parallel-group trial in approximately 1100 subjects with moderate to severe chronic plaque-type psoriasis. It is expected that subjects will be enrolled at approximately 200-250 study sites worldwide.

The study consists of 3 epochs: Screening (of at least 2 weeks and up to 4 weeks), Treatment epoch (of 52 weeks: from randomization to Week 52), and follow-up epoch (of 8 weeks: only for subjects with premature treatment discontinuation). An outline of the visits is presented [Figure 3-1](#), while a detailed visit and assessment schedule can be found in [Table 6-1](#).

Safety and efficacy assessments will be performed according to the visit schedule ([Table 6-1](#)).



Figure 3-1 Study design



BSL = Baseline; EOT = end of treatment epoch

1 = ustekinumab dose is based on body weight at baseline; 45 mg for subject \leq 100 kg; 90 mg for subject $>$ 100 kg

2 = for subjects with premature treatment discontinuation only

↓ = active dose administration; in order to keep the blind, subjects will receive placebo administrations at several time points (not shown in this study design figure)

Screening (Screening to Randomization)

The screening epoch of at least 2 weeks and up to 4 weeks will be used to assess the subject's eligibility and to taper subjects off prohibited medications.

Treatment Epoch (Randomization to Week 52)

The Treatment Epoch is the period from randomization (baseline) through Week 52. At the start of the treatment epoch, eligible subjects will be randomized in a 1:1 ratio to one of the two double-blind treatment groups: secukinumab 300 mg s.c. and ustekinumab 45 mg or 90 mg s.c. (depending upon weight at randomization).

The last dose will be administered at Week 48. The planned end of treatment epoch visit [EOT] will be performed at Week 52. The Week 52 visit should be the last visit of the study for subjects who complete the treatment epoch.

For all subjects who discontinue study treatment prematurely for any reason before the end of the treatment epoch the EOT visit should be performed approximately 4 weeks after their last dose of study drug and then subjects should enter the treatment free follow up epoch.

Follow-up epoch

Subjects who prematurely discontinue the treatment epoch will enter the treatment free follow-up epoch. The treatment free follow up visits (no study treatment administered during

the follow up epoch) should include F4 and F8 follow up visits. Follow up visit F4 is approximately 4 weeks after the EOT visit (that is 8 weeks after the last study treatment administration). Follow up visit F8 is approximately 8 weeks after the EOT visit (that is 12 weeks after the last study treatment administration).

3.2 Rationale for study design

The subject population will be described in more detail in the [Section 4](#) below.

The randomized, double-blind, parallel-group, and comparator-controlled design used in this study is aligned with previous studies performed in the indication of plaque psoriasis such as the ACCEPT study ([Griffiths et al 2010](#)), the PHOENIX 1 ([Leonardi et al 2008](#)) and the PHOENIX 2 studies ([Papp et al 2008](#)), the CLEAR study ([Thaci et al 2015](#)) as well as the European Medicines Agency (EMA) Guidelines for the Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis ([CHMP/EWP/2454/02 2004](#)).

The co-primary endpoints being the PASI 90 and IGA mod 2011 0/1 responses have been chosen as these come closer to the total or almost total clearance of psoriatic lesions, the ultimate goal of treatment. The CHMP guidance indicates that a PASI 90 response is the “best evidence” of efficacy and is considered an appropriate measure of “Treatment Success”. Furthermore, PASI 90 seems to be the new treatment target in a new era with more efficacious biologics, since it is being used more frequently as primary endpoint in the more recent psoriasis trials.

Finally, PASI 90 response rates observed in the phase III studies were closer to the endpoint of “clear/almost clear skin” (IGA mod 2011 0/1) than PASI 75. Further, the study design and study endpoints have been discussed and agreed with the US FDA.

The primary endpoint of the trial is at Week 12. This time point was chosen because the efficacy of psoriasis systemic treatment is generally established between 12 and 16 weeks. The Week 12 timepoint was the timing of the primary endpoint used within the registration phase III programs for the approval of both secukinumab and ustekinumab, and is therefore used as the primary comparison. The Week 16 timepoint is used as a secondary endpoint, because that is the time point at which secukinumab reaches its highest efficacy.

Furthermore, this study design also allows for the assessment of long-term (one full year) safety and efficacy of secukinumab 300 mg compared to ustekinumab administered according to its approved labeling.

The study has a double-blind design to be aligned with the above listed guideline. Due to differences in the appearance of the packaging and the final dose forms of secukinumab and ustekinumab, precautions have been taken to ensure that investigators/site personnel and subjects remain blind to treatment allocation during entire treatment and follow-up epoch. The details are provided in [Section 5.4](#) (Treatment blinding).

The regular assessments of disease activity, clinical status and safety parameters ensure that safety is monitored closely and both the subject and the investigator have the opportunity to assess if their continued participation in the study is to their benefit. If the subject’s participation is deemed not to be of continued benefit by either the investigator or the subject, the subject may freely exit the study at any time.



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

The dose regimens selected for secukinumab and ustekinumab are as per the approved label for the respective drugs in various countries i.e. 300 mg for secukinumab (the recommended dose within approved product labelling), and dosing per weight group for ustekinumab.

The proposal is to use secukinumab at a dose of 300 mg administered subcutaneously with a weekly regimen (Baseline/randomization, Week 1, Week 2, and Week 3) followed by treatment every 4 weeks thereafter (starting at Week 4) per approved dose of secukinumab in moderate to severe plaque psoriasis.

Ustekinumab will be administered at Baseline, Week 4 and then every 12 weeks as per the approved dose regimen for treatment of patients with moderate to severe plaque psoriasis: for patients weighing ≤ 100 kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks; for patients weighing >100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

3.4 Rationale for choice of comparator

An active comparator arm has been chosen for this study rather than a placebo arm. Ustekinumab is a fully human monoclonal anti-human IL-12/23 antibody of the IgG1/ κ -class which has been commercially available for a number of years and has proved to be a safe and efficacious treatment for moderate to severe plaque psoriasis.

The efficacy of ustekinumab has been demonstrated in plaque psoriasis in a number of placebo-controlled trials including PHOENIX 1 and PHOENIX 2, and in a controlled Phase III trial versus etanercept (ACCEPT) (Leonardi et al 2008; Papp et al 2008; Griffiths et al 2010). PASI 90 response rates of approximately 42% were reported with ustekinumab (combined doses) in pivotal studies (PHOENIX 1, PHOENIX 2 and ACCEPT) after 12 weeks of treatment.

Based on the available data, ustekinumab is considered as an established, appropriate, and reliable comparator drug. It has been used as a comparator for secukinumab in a previous study (CAIN457A2317/CLEAR). This study, CLARITY, intends to confirm the comparative efficacy and safety observed in the CLEAR study.

3.5 Purpose and timing of interim analyses/design adaptations

Week 16 analysis will be performed after all subjects have completed the Week 16 visit.

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 was initially approved in 2014 in Japan, followed by other markets such as the US, EU, Canada and Switzerland for the treatment for moderate to severe plaque psoriasis in adults. The approved forms of secukinumab 150 mg are 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 II and III clinical studies in adults have not shown any impediment to using secukinumab subcutaneously in man. In total 4546 patients with moderate to severe plaque psoriasis were included in studies in the registration program. This included 3430 patients treated with secukinumab in 10 phase II/III studies, 2727 of whom were treated for at least 6 months and 2029 of whom were treated for at least 48 weeks.

In adult studies, secukinumab has shown a very good efficacy profile in the treatment of moderate to severe chronic plaque psoriasis. Superiority of secukinumab 150 mg and 300 mg doses 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). Secukinumab at both doses was also found to be superior in efficacy compared to etanercept with a rapid onset of action in the etanercept and placebo-controlled studies, CAIN457A2302 and CAIN457A2303. The safety data from the completed and ongoing studies including AE and SAE data, laboratory parameters and immunogenicity data demonstrate a good safety profile which included an observed risk of infections in particular *Candida* infections and neutropenia (without association with serious infections) 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 timely associated with non-serious infections.

The approved product labelling reflects the identified risks for the product; subsequent safety data including (1) AE data, laboratory parameters, available immunogenicity data from the completed studies, and (2) SAE data from the phase III studies do not highlight any new individual safety risk or particular pattern of event clustering.

Subjects with pre-existing malignancies within the past 5 years are generally excluded from studies with secukinumab although there is no scientific basis to suggest that secukinumab would increase the risk for malignancies. Indeed, the majority of preclinical data, available in the literature, suggest that blocking IL-17A may actually prevent tumor growth.

Based upon the results of toxicology studies which demonstrated a lack of effect of secukinumab on fertility and embryo-fetal development, women of childbearing potential can be included in studies with secukinumab, however, pregnancy should be avoided by proven effective measures. No contraceptive measures are required for males participating in studies with secukinumab.

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

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

Additional information can be found in the IB for secukinumab.

4 Population

The study population will consist of a representative group of male and female subjects (≥ 18 years old) with moderate to severe plaque psoriasis that is inadequately controlled by topical treatments (including topical corticosteroids), ultraviolet (UV) light or systemic therapy (including biologic therapy) and requires systemic therapy.

It is aimed to randomize a total of approximately 1,100 subjects in around 200 -250 centers worldwide. 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. Subjects must be able to understand and comply with the requirements of the study and communicate with the investigator, and must give a written, signed and dated informed consent before any study related activity is performed. Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations
2. Men or women must be at least 18 years of age at the time of screening
3. Chronic plaque-type psoriasis present for at least 6 months and diagnosed before randomization
4. Moderate to severe plaque psoriasis as defined at randomization by:
 - PASI score of ≥ 12 **and**
 - Body Surface Area (BSA) affected by plaque-type psoriasis $\geq 10\%$ **and**
 - IGA mod 2011 ≥ 3 (based on a scale of 0–4)
5. Candidate for systemic therapy, defined as having psoriasis inadequately controlled by:
 - Topical treatment (including topical corticosteroids) **and/or**
 - Phototherapy **and/or**
 - Previous systemic therapy

4.2 Exclusion criteria

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

1. Forms of psoriasis other than plaque psoriasis (e.g., pustular psoriasis, erythrodermic and guttate psoriasis)
2. Drug-induced psoriasis (e.g., new onset or current exacerbation from β -blockers, calcium channel inhibitors or lithium)
3. Ongoing use of prohibited treatments. Washout periods detailed in the protocol must be adhered to ([Table 5-2](#)). 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.

Note: administration of live vaccines within 6 weeks prior to Randomization or during the study period is also prohibited. Further BCG vaccine should not be given for one year

prior to randomization or during treatment or for one year following discontinuation of treatment.

4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17RA, or ustekinumab
5. Use of any other investigational drugs within 5 half-lives of the investigational treatment before study drug initiation or until the pharmacodynamics effect has returned to baseline, whichever is longer
6. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test
7. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g. 20 weeks in EU). Effective contraception methods include:
 - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
 - Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
 - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
 - Barrier methods of contraception: condom or occlusive cap. For UK: with spermicidal foam/gel/film/cream/vaginal suppository.
 - Use of oral, injected or implanted hormonal methods of contraception or other forms or hormonal contraception that have comparable efficacy (failure <1%), e.g., 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.

NOTE: Women are considered post-menopausal and not of childbearing potential if they have had:

- 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms), or
 - Surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 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 is she considered not of child-bearing potential.
8. 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 render 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.

9. Investigator discretion should be used for subjects with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders
10. Presence of
 - Significant medical problems, including but not limited to the following: uncontrolled hypertension (systolic ≥ 160 mmHg and/or diastolic ≥ 95 mmHg), congestive heart failure (New York Heart Association [NYHA] status of class III or IV)
 - Serum creatinine level exceeding 2.0 mg/dL (176.8 $\mu\text{mol/L}$)
 - Total white blood cell (WBC) count $<2,500/\mu\text{L}$, platelets $<100,000/\mu\text{L}$, neutrophils $<1500/\mu\text{L}$ or hemoglobin <8.5 g/dL, at screening
11. Active systemic infections during the 2 weeks prior to randomization (exception: common cold) or any infection that reoccurs on a regular basis; investigator discretion should be used regarding subjects who have traveled or resided in areas of endemic mycoses, such as histoplasmosis, coccidioidomycosis or blastomycosis and for subjects with underlying conditions that may predispose them to infection, such as advanced or inadequately controlled diabetes
12. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive or indeterminate QuantiFERON TB-Gold test (QFT) at screening. Subjects with a positive QFT test may participate in the study if a full tuberculosis work up (according to local practice/guidelines) completed within 12 weeks prior to randomization establishes conclusively that the subject has no evidence of active tuberculosis. If the presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local country guidelines for at least 4 weeks prior to randomization.
13. Past medical history record of, or current infection with, human immunodeficiency virus (HIV), hepatitis B or hepatitis C prior to randomization
14. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for skin Bowen's disease, 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)
15. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
16. History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to randomization
17. History of hypersensitivity to any of study drug constituent

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The following study drugs will be used:

- Investigational treatment
 - Secukinumab 150 mg, 1 ml liquid formulation in a pre-filled syringe
- Control treatment
 - Secukinumab placebo, 1 ml liquid formulation in a pre-filled syringe
 - Ustekinumab 45 mg, 0.5 ml liquid formulation in a pre-filled syringe

Investigational treatment: secukinumab

Secukinumab for s.c. injection is provided in a pre-filled syringe containing 150 mg secukinumab. Each 300 mg dose is given as two s.c. injections of 150 mg.

Control treatment:

- Secukinumab placebo: secukinumab placebo to 150 mg secukinumab for s.c. injection is provided in a matching pre-filled syringe. Each pre-filled syringe contains a mixture of inactive excipients, matching the composition of the secukinumab 150 mg dose.
- Ustekinumab is provided in a pre-filled syringe containing 45 mg of ustekinumab for s.c. injection. Subjects weighing >100 kg at baseline will receive a dose of 90 mg according to the label, which consists of two 45mg pre-filled syringes.

Secukinumab pre-filled syringes 150 mg and secukinumab pre-filled syringes placebo will be supplied by Novartis.

Ustekinumab pre-filled syringes 45 mg will be supplied by Novartis from US market source.

All study drugs will be labeled appropriately.

The removable cap of the secukinumab pre-filled syringe contains a derivative of natural rubber latex. Although no natural rubber latex is detected in the cap, the safe use of the secukinumab 1 mL pre-filled syringe in latex-sensitive individuals has not been studied.

5.1.2 Additional treatment

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

5.2 Treatment arms

Subjects will be randomized to one of the following two treatment arms in a ratio of 1:1. In order to achieve a balanced weight distribution in each treatment arm, randomization in these two arms will be stratified by body weight (≤ 100 kg and > 100 kg) at baseline.

- **Secukinumab arm:** will receive a dose of secukinumab 300 mg s.c. which consist of two injections of the 150 mg pre-filled syringes at a frequency shown in [Table 5-1](#)
- **Ustekinumab arm:**

- Subjects weighing >100 kg at baseline will receive a dose of 90 mg ustekinumab s.c., which consists of two injections of the 45 mg pre-filled syringe at a frequency shown in [Table 5-1](#)
- Subjects weighing ≤ 100 kg at baseline will receive a dose of 45 mg ustekinumab s.c., which consist of one injection of the 45 mg pre-filled syringe + one secukinumab placebo s.c. injection at a frequency shown in [Table 5-1](#)

In addition, in order to maintain the blind, placebo injections matching the secukinumab 150 mg pre-filled syringe will be given to subjects in the ustekinumab arm at various time points, as can be seen in [Table 5-1](#) so that all subjects will receive 2 s.c. injections at each dosing time point.

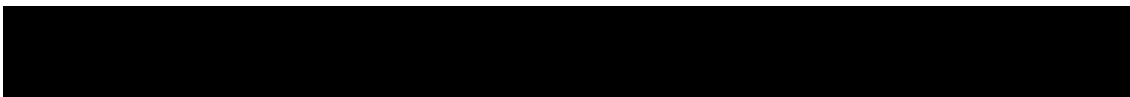
Further, the pre-filled syringes for secukinumab and ustekinumab have a different outward appearance. Therefore, as this is a double-blind study, the dispensing and administration of the study treatments will be performed at the study site by suitably qualified unblinded personnel who are otherwise not involved in study conduct. Further details are provided in [Section 5.3](#), [Section 5.4](#) and [Section 5.5](#).

Table 5-1 Overview of treatment during the study – type and number of injections

Epoch	Treatment*															
Week (relative to randomization)	R	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48
Secukinumab 300 mg																
Active injection ¹	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Ustekinumab²																
Subject ≤ 100 kg																
Active injection ²	1	-	-	-	1	-	-	1	-	-	1	-	-	1	-	-
Placebo injection ³	1	2	2	2	1	2	2	1	2	2	1	2	2	1	2	2
Subject > 100 kg																
Active injection ²	2	-	-	-	2	-	-	2	-	-	2	-	-	2	-	-
Placebo injection ³	-	2	2	2	-	2	2	-	2	2	-	2	2	-	2	2
¹ Secukinumab 150 mg pre-filled syringes: subjects randomized to secukinumab will receive 2 active injections; ² Ustekinumab dose based on body weight at baseline: 45 mg for subject ≤ 100 kg (1 active injection); 90 mg for subject > 100 kg (2 active injections) ³ Secukinumab placebo pre-filled syringes * Treatment epoch is from randomization until Week 52 (last dose given at Week 48)																

5.3 Treatment assignment and randomization

At the Randomization Visit (Day 1), all eligible subjects will be randomized via IRT system to one of the two treatment arms. The unblinded pharmacist or other unblinded qualified site personnel will contact the IRT provider after the investigator has confirmed that the subject fulfills all the inclusion/exclusion criteria. The IRT system will assign a randomization number to the subject, which will be used to link the subject to a treatment arm, and will



dispense a unique medication number of investigational treatment to the subject. The randomization number will not be communicated to the user.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator or staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that generates unique medication numbers. The randomization scheme for subjects will be reviewed and approved by a member of the Audit Readiness, Validation & Randomization Group [REDACTED].

Randomization will be stratified by body weight assessed at Day 1. Stratification ensures a balanced allocation of subjects to treatment groups within the two weight strata: “body weight ≤ 100 kg” or “body weight > 100 kg”. It is expected that approximately 40% of the subjects will be in the upper weight stratum.

5.4 Treatment blinding

All data up to Week 16 will be collected with the Novartis clinical trial team (or delegates), investigators/site personnel evaluating subjects and subjects blinded to treatment allocation. The designated Novartis personnel will be unblinded following DB lock for the interim analysis after all subjects have completed Week 16. Field monitors/clinical research associates will remain blinded until after Final DB lock. All blinded site personnel, including the assessor performing the study assessments will remain blinded to individual treatment allocation until after Final DB lock using the following methods:

- Randomization data will be kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:
 - Specific vendors whose role in trial conduct requires their unblinding (e.g., IRT)
 - DSM (Drug Supply Management)
- Study medication will be dispensed by an unblinded pharmacist (or other unblinded qualified site personnel) who is independent of those involved in the assessment of study subjects. In addition the unblinded pharmacist (or other unblinded qualified site personnel) will store study medication and keep medication records containing unblinded information in a separate area to which blinded staff would not have access.
 - Study treatments will be administered by an “independent study drug administrator”: an unblinded suitably qualified individual (nurse, physician, or other unblinded qualified site personnel) who is not responsible for any aspect of subject assessment or follow-up. The “Independent study drug administrator” could be the same person dispensing the drug if suitably qualified to perform both activities.
 - prior to the administration, the unblinded site personnel will put in place all methods e.g. physical barriers as agreed with the subject and



- being available at the site to prevent subject seeing the appearance of their study treatment
- the individual administering study treatment will be advised to refrain from making any comments to study staff or to other subjects regarding the appearance of study treatments
- the procedural details relating to treatment blinding and blinded drug administration will be described in a manual which will be provided separately

In the event that the packaging of a study treatment has a broken seal, this information will be documented in the IRT, along with a reason (if applicable) and the medication number so that the syringe will not be available to dispense to another subject.

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

However once a subject comes to the last study visit (Week 52 or F8 as applicable), (s)he will be unblinded 'on demand' to support an informed decision on how to manage the subject post-study. This will be a subject-by-subject approach and will be permitted only after Week 16 DB lock is achieved. For subjects who withdraw consent earlier and do not attend the F8 visit this could be done at the visit when he/she withdrew consent; however the information will not be shared with the subject before the Week 16 DB lock. When the subject is unblinded, the information should preferably not be shared with the investigator. Instead, it is preferred that the physician treating the subject after last study visit is a person not involved in the study conduct. The blinding is maintained beyond Week 16 to ensure reliable evaluation of efficacy and safety measures for the complete duration of treatment.

5.5 Treating the subject

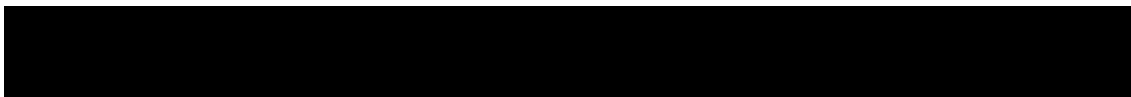
Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Subject numbering

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

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

If the subject is randomized but 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 Screening epoch Study Disposition CRF.



5.5.2 Dispensing the study drug

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

Ustekinumab pre-filled syringes 45 mg will be supplied by the Novartis Drug Supply Management (DSM) team and should be dispensed as per label requirements.

The secukinumab active and placebo and ustekinumab treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 2 treatment arms. The unblinded site pharmacist or unblinded qualified site personnel 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, the unblinded site pharmacist or unblinded qualified site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by designated unblinded site personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the unblinded site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO 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 study treatments, i.e. secukinumab pre-filled syringes (150 mg active/placebo) and ustekinumab pre-filled syringes (45 mg active) must be stored in a locked refrigerator at 2-8°C (36-46°F), and protected from light and must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations. Study treatments should not be frozen.

The unblinded pharmacist or other unblinded qualified site personnel 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 unblinded monitors during site visits or remotely and at the completion of the trial.

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

All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

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

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

All doses of study treatment are to be administered at the study site and should be performed after the study assessments for the visit have been completed. The first study treatment administration will occur at the randomization visit after inclusion/exclusion criteria have been confirmed, all study scheduled assessments have been performed and the scheduled blood samples have been drawn.

At all study site visits when pre-dose blood samples have to be drawn (Table 6-1), the study treatment will be injected only after the blood samples have been taken. At all site visits when study assessments need to be done, all study assessments, [REDACTED] should be completed prior to the injection of study treatment.

The study treatment solution must be injected in non-affected areas of the skin into the appropriate body site (thigh, abdomen, upper outer arm). If possible, throughout the trial administer the study treatment rotating the injection site from visit to visit and also for each injection at a given visit.

Prior to administration, the boxes containing the PFS with study treatment solution should be allowed to come to room temperature, unopened.

Used PFS should be disposed immediately after use in a sharps container **OR** according to the regulatory needs of the respective countries.

The investigator must promote compliance by instructing the subject to attend the study visits as scheduled and by stating that compliance is necessary for the subject's safety and the validity of the study.

Study treatment administration

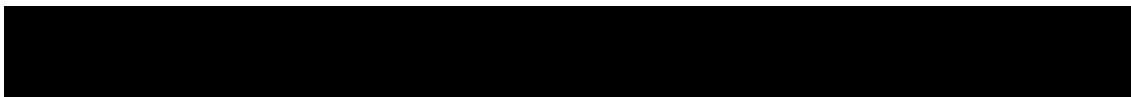
All study treatment must be administered at the site and will be administered by unblinded site personnel not responsible for any aspect of subject assessment or follow-up (Section 5.4)

Instructions mentioned in Section 5.4 must be followed to avoid unblinding. The type and number of injections to be administered are detailed in Table 5-1.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment interruptions are not permitted.

No dose adjustment of study treatment is permitted and there should be no interruption of the study treatment during the study. However a positive urine pregnancy test during the treatment epoch of the study requires immediate interruption of study treatment until serum β -



hCG is performed and found to be negative. If the serum β -hCG test is positive, study treatment must be definitively discontinued.

If a dose (secukinumab or placebo secukinumab) was dispensed by IRT but not administered to a subject at a visit at which the subject attended, this deviation event must be recorded on the Dosage Administration Record CRF.

5.5.6 Rescue medication

Use of rescue medication is not permitted during the study.

5.5.7 Concomitant medication

All treatments administered during the 6 months prior to start of study treatment (including any treatments started during the screening epoch) for any reason NOT including psoriasis will be entered in the Prior and Concomitant Medication eCRF. The start date, end date, dose, unit, frequency, route and reason for administration or change are to be recorded.

In addition, psoriasis treatments used from the time subject started to treat psoriasis will be reported on the Prior Psoriasis Therapy eCRF. All topical treatments, systemic treatments and phototherapies for psoriasis administered prior to Randomization Visit will be entered in the Prior Psoriasis Therapy eCRF page ([Section 6.2.2](#)).

The investigator/qualified site staff should instruct the subject to notify the study site about any new medications that he/she takes after being enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject starts study treatment must be listed on the eCRF.

5.5.7.1 Permitted concomitant medications (not for psoriasis or psoriatic arthritis)

Concomitant medications are allowed if not listed in [Table 5-2](#). Dose adjustments of these medications should be avoided during the study. If a dose adjustment of these medications does occur, they must be recorded on the Prior and Concomitant Medication eCRF.

Subjects who are receiving treatments known to worsen psoriasis (e.g. beta-blockers, lithium) should be on a stable dose for at least 4 weeks before Randomization Visit.

Mild to moderate topical corticosteroids (TCS) are allowed only during the screening epoch if used only on the face, scalp, and/or genitoanal area. Subject should stop use of these TCS at least the day preceding the randomization visit.

TCS will be allowed after the Week 16 visit (timing of analysis of several key secondary endpoints) to the last study visit, only if:

- medication is started after the week 16 visit is completed;
- medication is used for **14 consecutive calendar days or less**;
- medication is used for an indication **other than psoriasis and not on the area affected with psoriasis**.

Use of these TCS must be recorded on the Concomitant Medication-Topical Corticosteroid eCRF.

5.5.7.2 Permitted concomitant medications for psoriasis

After the screening epoch, the use of concomitant medication for psoriasis in all body regions is restricted to bland emollients (not supplied by Novartis) and other non-medicated interventions (not listed in [Table 5-2](#)). Use of bland emollients must be recorded on the Concomitant medications eCRF. Use of any other non-medicated interventions must be recorded on the Procedures and Significant non-drug therapies eCRF.

The definition of “bland” excludes all topical medications that contain pharmacologically active ingredients such as (but not limited to) lactic acid, salicylic acid, urea, α -hydroxy acids or fruit acids.

The use of bland emollients should be avoided during the 12 hours preceding a scheduled study visit.

5.5.8 Prohibited medication

Use of any treatments displayed in [Table 5-2](#) that could confound the efficacy assessments are NOT allowed during the study for any indication and wash-out periods for these treatments are indicated in [Table 5-2](#). If the use of these treatments is required, then the subject must NOT be randomized into the study.

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

If a prohibited treatment listed in [Table 5-2](#) was used during the study, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study. At the discretion of the investigator/qualified site staff, if the subject’s use during the study of a prohibited treatment listed in [Table 5-2](#) presents undue safety risk for the subject, the subject should be discontinued from study treatment according to [Section 5.6.2](#). If the subject received a live virus vaccination during the study, the subject must discontinue study treatment and complete the end-of-treatment epoch visit (Week 52/EOT) and Follow-up visits F4 and F8.

Table 5-2 Prohibited medication

Prohibited treatments ^{1, 2}	Washout period (before Randomization Visit)
Ustekinumab	No prior use allowed
Secukinumab	No prior use allowed
Any biologic drug directly targeting IL-17 or the IL-17 receptor (other than secukinumab e.g., brodalumab, ixekizumab)	No prior use allowed
Any biologic directly targeting IL-12/23 other than ustekinumab (e.g. briakinumab) or IL-23 (e.g. guselkumab, tildrakizumab)	6 months
Alefacept, efalizumab	6 months



Biological immunomodulating agents other than above (e.g., adalimumab, etanercept, infliximab)	12 weeks
Other systemic immunomodulating treatments ³ e.g., MTX, cyclosporine A, corticosteroids (oral, i.v., intramuscular, s.c., intra-articular, transdermal), cyclophosphamide	4 weeks
Other systemic psoriasis treatments (e.g. retinoid, fumarates, apremilast)	4 weeks
Photo-chemotherapy (e.g., PUVA)	4 weeks
Phototherapy (e.g., UVA, UVB)	2 weeks
Topical treatment that is likely to impact signs and symptoms of psoriasis (e.g., corticosteroids ^{4,5} , vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α -hydroxy or fruit acids)	2 weeks
Live virus vaccinations ^{6,7}	6 weeks
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Any other treatment known to worsen psoriasis (e.g., beta-blockers, calcium channel blockers, lithium)	Stable at least 4 weeks before randomization

¹ If the prohibited treatment is being used during the study for any indication, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study.

² In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator/qualified site staff.

³ Inhaled CS as well as corticosteroid drops in the eye or ear or nasal sprays with only a topical effect (e.g., to treat asthma) are not considered “systemic immunomodulating treatments” and are therefore acceptable as co-medication.

⁴ Mild to moderate topical corticosteroids are allowed only during the screening epoch if used only on the face, scalp, and/or genitoanal area and should not be used at least the day preceding the randomization visit.

⁵ Topical corticosteroids and other topical treatments will be allowed during treatment and follow-up epoch if (**all must apply**):

- medication is started after the Week 16 visit is completed; **and**
- medication is used for 14 consecutive calendar days or less; **and**
- medication is used for an indication other than psoriasis and not on the area affected with psoriasis

⁶ If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

⁷ BCG vaccine should not be given for one year prior to randomization, during treatment and one year following discontinuation of treatment.

Exposure to light

Subjects need to be advised to limit exposure to ultraviolet (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 procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available and applicable)
- subject 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 unblinding can be performed at any time.

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

The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason (except for 'on-demand' unblinding after completion of last study visit as mentioned in [Section 5.4](#)).

Subjects who are discontinued from study treatment are requested to return for the end of treatment epoch visit (Week 52/EOT) and Follow-up visits F4 and F8.

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.

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, and can be initiated by either the subject or the investigator.

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

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

Study treatment must be discontinued under the following circumstances:

- 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.
- Any laboratory abnormalities that in the judgment of the investigator/qualified site staff, taking into consideration the subject's overall status, prevent the subject from continuing study treatment.
- Pregnancy (see [Section 6.5.6](#) and [Section 7.4](#))
- Ongoing use of prohibited treatment per recommendations in [Table 5-2](#)
- Any situation in which study participation might result in a safety risk to the subject
- Emergency unblinding

If discontinuation of study treatment occurs for any reason, the subject should NOT be considered withdrawn 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 eCRF. The investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the eCRF.

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 in EOT Visit Week 52 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 EOT Visit Week 52 assessments.

The investigator/qualified site staff must contact the IRT when the subject completes the EOT Visit Week 52 assessments to register the subject's early completion of the study due to study treatment discontinuation.

Further subject should also return for the final Follow-up visits, F4 (8 weeks after last study treatment) and F8 (12 weeks after last study treatment) as per [Table 6-1](#).

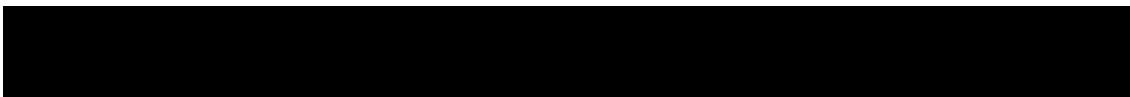
After study treatment discontinuation, at a minimum, the following data should be collected at site visits or via telephone visits:

- new/concomitant treatments
- Adverse Events/Serious Adverse Events

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

If study drug discontinuation occurs because treatment code has been broken, please refer to [Section 5.5.9](#)



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 [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 should 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 (i.e. planned Week 52 visit).

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 enrolment). 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 assessments and indicates with an “X” when the visits are 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. Every effort should be made to respect the time frame for any visits, particularly the Week 4, Week 12, Week 16 and Week 52 visit.

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 subjects, the investigator/qualified site staff will record if the subject was rescreened on the rescreening CRF and any applicable screening numbers 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. For rescreening, all screening assessments must be performed 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 epoch, subjects may be seen at an unscheduled visit, e.g. if they experience deterioration of psoriasis or suspected AEs. During these unscheduled visits, study treatment will NOT be administered.

For subjects who discontinue study treatment prematurely before the end of the treatment epoch for any reason other than withdrawal of informed consent or lost to follow up, the Week 52 (planned EOT) visit must be performed.

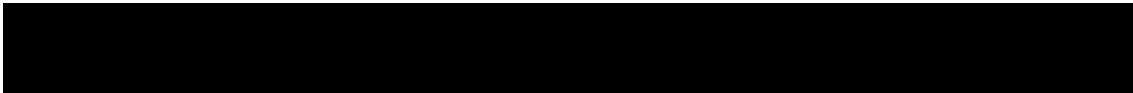
Further such subjects should also return for the additional Follow-up visits F4 and F8 (8 and 12 weeks after last study treatment respectively, see Table 6-1).

If a subject refuses to return for these assessments or is unable to do so, every effort should be made to contact them, or a knowledgeable informant, by telephone or by sending appropriate correspondence (i.e. certified letter) immediately. At this contact, the safety (e.g. potential occurrence of AEs or SAEs) and the primary reason for the subject’s premature withdrawal should be determined. Documentation of attempts to contact the subject should be recorded in the subject source documents.



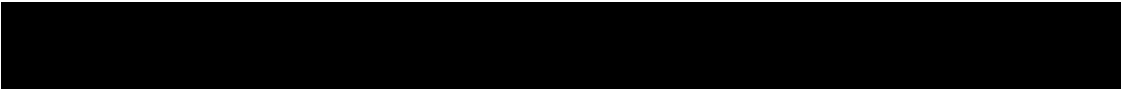
Table 6-1 Assessment schedule

Epochs	Screen	Treatment																		FU		Unscheduled visit ¹⁰
		Week (relative to randomization)	≥-4 to ≤-2	R	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52 EOT	F4 ⁸	
Assessment Day	≥ - 28 to ≤ - 14	1	8	15	22	29	57	85	113	141	169	197	225	253	281	309	337	365	NA	NA	NA	
Obtain informed consent	X																					
Demographics	X																					
Inclusion/exclusion criteria ¹	X	X																				
Smoking history	X																					
Psoriasis: medical history/previous psoriasis therapies	X																					
Cardiovascular medical history	X																					
Other medical history and prior medications	X																					
Concomitant medications	Update as necessary																					
(s)AE assessment	Update as necessary																					
Physical examination	S							S					S						S			S
Height	X																					
Weight	X	X						X					X			X			X			X
Vital signs	X	X				X		X	X				X			X			X	X	X	X
Laboratory sampling: safety panel ² (Clinical chemistry, hematology)	X	X						X					X						X			X
Urinalysis	X																					X



Epochs	Screen	Treatment																		FU		Unscheduled visits ¹⁰
		≥-4 to ≤-2	R	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52 EOT	F4 ⁸	F8 ⁸	
Week (relative to randomization)	≥ -4 to ≤ -2	R	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52 EOT	F4 ⁸	F8 ⁸	Unscheduled visits ¹⁰	
Assessment Day	≥ -28 to ≤ - 14	1	8	15	22	29	57	85	113	141	169	197	225	253	281	309	337	365	NA	NA	NA	
Fasting labs: fasting plasma glucose and lipid panel ²		X																			X	
QuantiFERON® TB-Gold In-tube test ³	X																				X	
Serum pregnancy test ⁴	X																				X	
Urine pregnancy test (local) ⁵		X																X			X	
ECG (standard 12-lead) ⁶	S																				S	
PASI	X	X				X		X	X			X			X			X	X	X	X	
BSA	X	X																				
IGA mod 2011	X	X				X		X	X			X			X			X	X	X	X	
Randomization via IRT		X																				
Administer study treatment at study site ⁷		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Complete screening epoch eCRF	X																					
Complete end of treatment epoch eCRF																		X				
Complete Follow-up epoch eCRF ⁹																				X		

(s)AE: (serious) adverse event; BSA: Body Surface Area; ECG: electrocardiogram; eCRF: electronic case report form; IGA: Investigator's Global Assessment; IRT: interactive response technology; PASI: Psoriasis Area and Severity Index; R: randomization; TB: tuberculosis
X = assessment to be recorded on clinical database; S = assessment to be recorded on source documentation



1. These assessments are supported by and stored within the source documentation. Data relating to inclusion/exclusion criteria are captured in the corresponding eCRF
2. Samples will be shipped to the central laboratory for analysis
3. A repeat QuantiFERON® TB-Gold In-Tube test is recommended if the result of the first QuantiFERON® TB-Gold In-Tube test is “indeterminate”. The subject must be referred for a follow-up tuberculosis workup (as per local guidelines) if either the first or the repeat test is “positive” or if the results of both tests are “indeterminate”. If the first test is indeterminate, the investigator may decide not to repeat the test and to proceed directly to the workup, though this is not recommended. The subject will not be eligible for randomization if “active tuberculosis is present” or if “latent tuberculosis is present” and is untreated according to local guidelines
4. Only for females of child-bearing potential.
5. In the event of a positive urine pregnancy test, study treatment must be withheld and a serum pregnancy test performed at the same visit. A urine pregnancy test is not required for a woman who is sterile or who is post-menopausal.
6. Any clinically significant ECG findings need to be reported in CRF as medical history or AE (depending upon time of assessment relative to Screening).
7. Study medication must be prepared and administered by suitably qualified unblinded personnel who are not responsible for any aspect of subject assessment or follow-up.
8. F4 and F8 visits are follow-up visits only for subjects who prematurely discontinue. F4 visit is to be conducted 8 weeks after last dose of study treatment (4 weeks after EOT visit) and F8 visit is to be conducted 12 weeks after last dose of study treatment (8 weeks after EOT visit).
9. Follow-up visits will be conducted only for subjects who prematurely discontinued study treatment.
10. Unscheduled visit: The assessment(s) performed at an unscheduled visit are at the investigator’s discretion.

6.1 Information to be collected on screening failures

All subjects who sign the informed consent but discontinue prior to randomization at Randomization Visit are considered to be screen failures.

If a subject discontinues prior to randomization, the IRT provider must be notified within 5 days, and the reason for the subject not being randomized will be entered on the Screening Phase Disposition eCRF. The Screening visit date, the Demography eCRF, the Informed Consent eCRF, the Inclusion/Exclusion eCRF, and the subject rescreening eCRF (if applicable) must be completed. The AE eCRF should be completed for any SAEs that occurred during the screening epoch. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. The withdrawal of consent eCRF must be completed if consent was withdrawn during the screening epoch before the subject was randomized.

For all subjects who sign the informed consent and entered into the next epoch of the study, all AEs **occurring after the informed consent is signed** will be recorded on the AE eCRF.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.2 Subject demographics/other baseline characteristics

All Baseline assessments should be performed prior to first study treatment administration. These may be in the screening epoch (e.g. demographics) or at the Randomization Visit [REDACTED] depending on the assessment.

6.2.1 Demographics

Subject demographic and baseline characteristic data will be collected at the screening visit. Data to be collected on all subjects include: date of birth, age, sex, race, ethnicity, as well as height and weight.

Subject weight (stratification variable) will be reassessed at Randomization visit, prior to randomization.

6.2.2 Psoriasis medical history/previous psoriasis therapies

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

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



6.2.3 Smoking history

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

6.2.4 Co-morbidities – cardiovascular medical history

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

6.2.5 Relevant medical history/current medical conditions

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

Significant findings that are observed after the subject has signed the informed consent form and that meet the definition of an AE must be recorded in the AE eCRF.

6.2.6 Prior and concomitant medications

Concomitant medications and prior medications taken over the 6 months preceding study enrollment will be captured at the screening visit, and updated at the randomization visit in the Prior and Concomitant Medication eCRF.

6.2.7 Determination of tuberculosis status

Determination of tuberculosis (TB) status will be required before administration of study treatment and should be performed as defined by local guidelines. TB status must be determined by medical history, signs, symptoms, and TB testing (QuantiFERON-TB Gold assay).

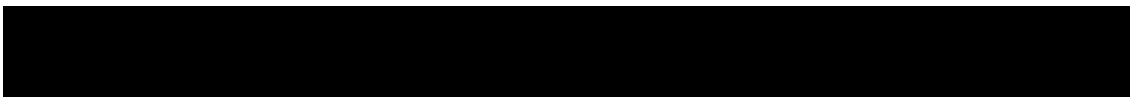
Any significant findings will be recorded in the Medical History eCRF, as necessary.

QuantiFERON TB-Gold In-Tube assay

A QuantiFERON® TB-Gold In-Tube assay will be performed to assess the TB status at screening for all subjects. This test will only be used to determine subject's eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection ([Doherty et al 2008](#)).

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

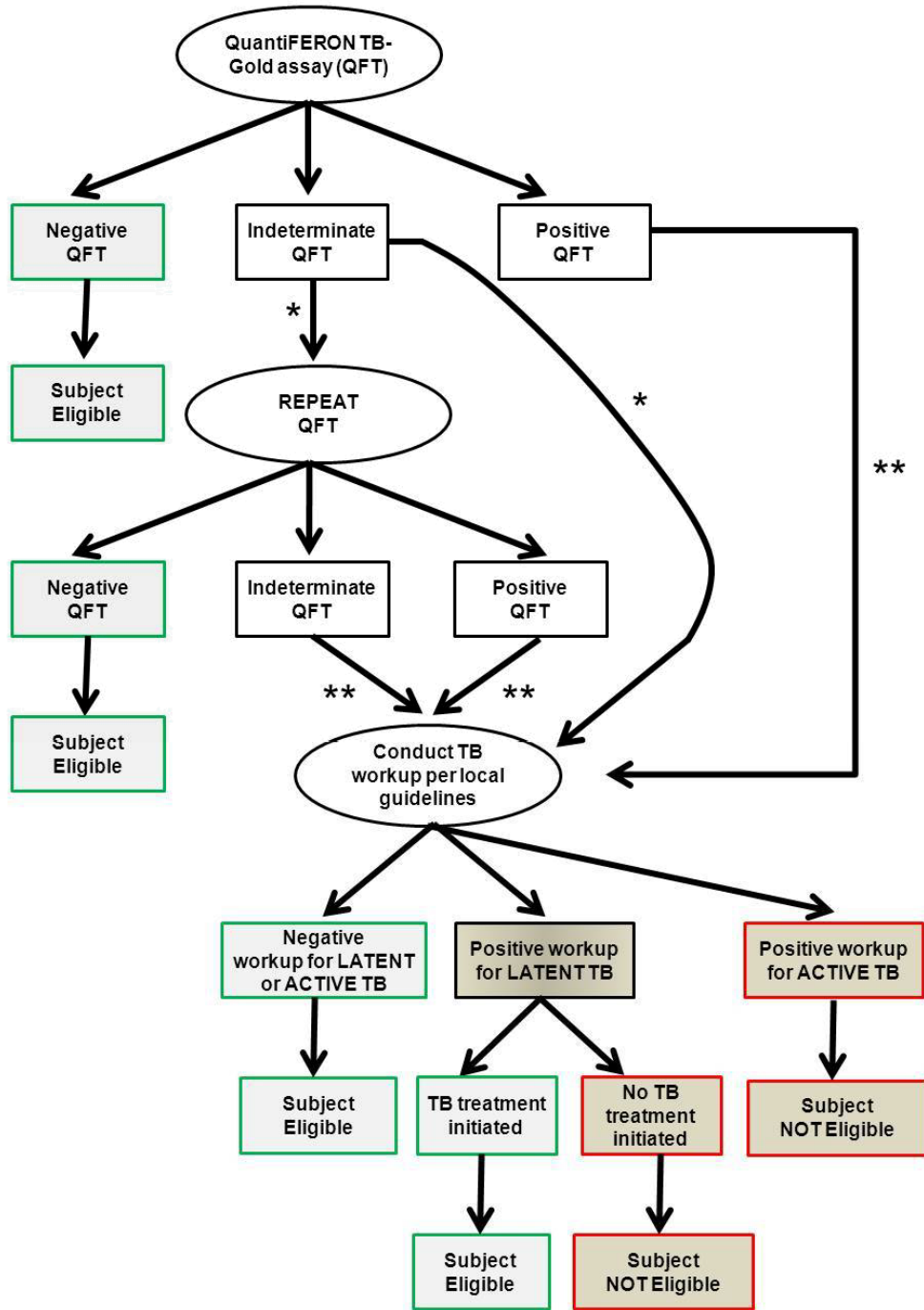
Furthermore, this test, in contrast to the purified protein derivative (PPD) skin test, is also insensitive to a booster effect since the subject is not exposed to the vaccine. The assay measures the production of interferon-gamma and presents it relative to a negative and a positive control sample ([Manuel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

- 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 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.
 - Subjects **positive** for latent TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration
 - Subjects **positive** for active TB per workup are not eligible for the study
 - Subjects **negative** for TB (no signs of latent or active TB) per workup may be randomized to the trial
- If the test result is **indeterminate**, it is **recommended to repeat the test once**. The investigator may decide to skip the repetition of the test and proceed directly to the workup (this is however not recommended). 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 or indeterminate, the investigator should perform workup per local guidelines. Subject 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. The subject will not be eligible for randomization if “active tuberculosis is present” or “latent tuberculosis is present” and is untreated per local guidelines.
 - 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.

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).

6.2.8 Other baseline characteristics

Baseline characteristic data to be collected on all subjects include (see also [Table 6-1](#)):

12-lead ECG (at screening), vital signs, hematology, clinical chemistry, physical examination, height, weight, past medical history record of HIV, Hepatitis B or C status, [REDACTED] as well as assessments of PASI, BSA and IGA mod 2011. A serum pregnancy test will be performed for women of childbearing potential.

All laboratory assessments are central except where indicated.

6.3 Treatment exposure and compliance

All doses of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page. Up to the Final DB lock, compliance will be assessed by unblinded field monitor at each visit using syringe (secukinumab, ustekinumab and secukinumab placebo) counts and empty medication boxes/outer packaging and information provided by the unblinded pharmacist or qualified site personnel responsible for treatment dispensation and preparation of the study medication.

6.4 Efficacy

All efficacy assessments should be performed prior to the administration of study treatment.

The recommended order for the efficacy assessments is described below.

[REDACTED]

- **Efficacy assessments**

The efficacy assessments should be completed in the following recommended order. In all cases, the assessor will be blind to treatment allocation:

- IGA mod 2011
- PASI

All remaining study visit procedures (e.g., laboratory sample collection, vital signs measurements) must be completed prior to administration of study treatment.

6.4.1 Investigator's Global Assessment (IGA mod 2011)

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

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

The IGA mod 2011 rating scale for overall psoriatic disease is shown in [Table 6-2](#).

[REDACTED]

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

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

Table 6-2 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

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

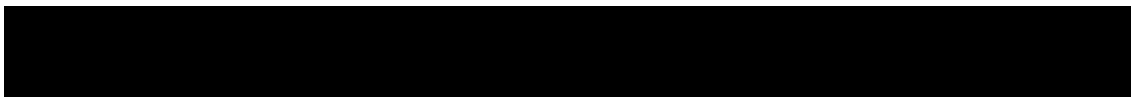
The investigator or trained qualified designee will complete the PASI assessment as indicated in [Table 6-1](#). Whenever possible, the same evaluator should perform this assessment at all visits.

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 full details of the 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 four 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 to help with the assessment are provided below:

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



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

$$\text{PASI} = 0.1(\text{E}_H + \text{I}_H + \text{D}_H)\text{A}_H + 0.2(\text{E}_U + \text{I}_U + \text{D}_U)\text{A}_U + 0.3(\text{E}_T + \text{I}_T + \text{D}_T)\text{A}_T + 0.4(\text{E}_L + \text{I}_L + \text{D}_L)\text{A}_L$$

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.

The baseline value for analysis of the PASI is collected at the Randomization Visit on the PASI score eCRF.

Subjects require a total BSA affected by plaque-type psoriasis of 10% or more and a PASI score of 12 or more at randomization to be eligible for this study.

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

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

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



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

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

Definitions of efficacy variables based on PASI

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

- **PASI 50 response (partial response):** subjects achieving $\geq 50\%$ improvement (reduction) in PASI score compared to baseline are defined as PASI 50 responders
- **PASI 75 response:** subjects achieving $\geq 75\%$ improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders
- **PASI 90 response:** subjects achieving $\geq 90\%$ improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders
- **PASI 100 response/remission:** complete clearing of psoriasis (PASI=0)

6.4.3 Appropriateness of efficacy assessments

PASI scores outcome measures, 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 mandated by the EMA for the clinical investigation of medicinal products for the treatment of psoriasis ([CHMP/EWP/2454/02 2004](#)).

As indicated in [Section 6.4.1](#), the IGA mod 2011 scale has been developed by Novartis in collaboration with health authorities, in particular the FDA. It is based on the previous version of the scale which was used in Phase II secukinumab studies, and has been used in all phase III studies. In the modified scale, the two "very severe" and "severe" have been condensed into a single category, "severe" and the explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points.

6.5 Safety

From Day 1, all blood draws and safety assessments must be performed prior to study treatment administration. Appropriate safety assessments (e.g., evaluation of AEs and SAEs) should be repeated after dosing with study treatment.

6.5.1 Physical examination

A physical examination, including general appearance, 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.

If 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 subject signing informed consent must be included in the Medical History eCRF. Significant findings made after the signing of

the informed consent which meet the definition of an AE must be recorded on the AE eCRF (Section 7).

6.5.2 Vital signs

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

After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic **blood pressure will be measured twice** (measurements separated by 1 to 2 minutes) using a validated device with an appropriately sized cuff and each BP measurement will be recorded in the source (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. Both measurements will be entered on the Vital Signs eCRF.

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

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

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

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

6.5.3 Height and weight

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

Height and body weight will be measured in indoor clothing, but without shoes.

If possible, body weight assessments should be performed by the same study site staff member and using the same scale throughout the study. The body weight recorded at Randomization visit will be used to stratify the subject population for randomization.

6.5.4 Laboratory evaluations

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

A central laboratory will be used for analysis of all specimens unless noted otherwise. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the Laboratory Manual.



For the identification of notable values, the laboratory manual should be consulted.

Whether action needs to be taken to address notable laboratory values will be decided by the investigator, taking into account the overall status of the subject. No specific action is foreseen as part of the study protocol.

6.5.4.1 Hematology

Hematology assessments will include hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count. Hematology assessments will be measured at all scheduled study visits specified in [Table 6-1](#).

6.5.4.2 Clinical chemistry

Serum chemistry will include blood urea nitrogen (BUN), creatinine, total bilirubin, alanine transaminase (ALT)/serum glutamic pyruvate transaminase (SGPT), aspartate transaminase (AST)/serum glutamic oxaloacetic transaminase (SGOT), gamma glutamyl transpeptidase (GGT), alkaline phosphatase. Serum chemistry will be measured at all scheduled study visits specified in [Table 6-1](#). Fasting plasma glucose and fasting lipids will be measured at baseline visit.

6.5.4.3 Urinalysis

Dipsticks will be provided by the central laboratory to the study sites for local urinalysis assessments. The sites will record the results in the Local Lab Results-Urinalysis eCRF page for each subject. Standard dipstick measurements for specific gravity, protein, glucose, pH, blood, urine blood (non-hemolyzed), urine blood (hemolyzed), bilirubin, ketones, WBC will be done at screening as indicated in [Table 6-1](#). If needed conditional microscopy assessments will be done.

6.5.5 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

A standard single 12-lead ECG will be collected at screening visit ([Table 6-1](#)). The investigator/qualified site staff must review and initial the tracing. The original ECGs appropriately signed, should be collected and archived at the study site.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant abnormalities should be recorded on the relevant section of the (cardiovascular) medical history/AE CRF/e(CRF) page as appropriate.



6.5.6 Pregnancy

A serum β -hCG test will be performed at screening in all pre-menopausal women who are not surgically sterile.

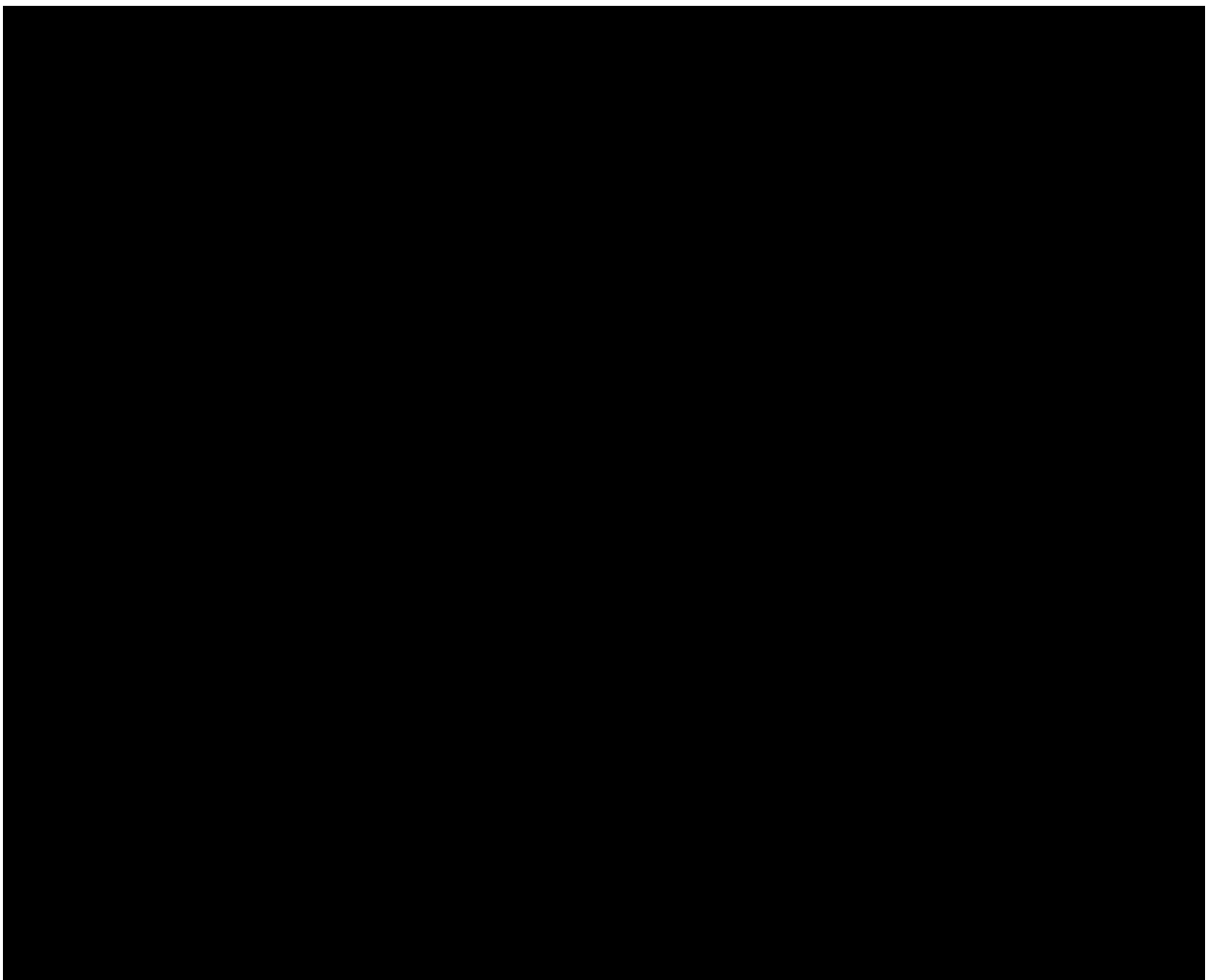
All women of childbearing potential will also have a urine pregnancy test performed locally at baseline.

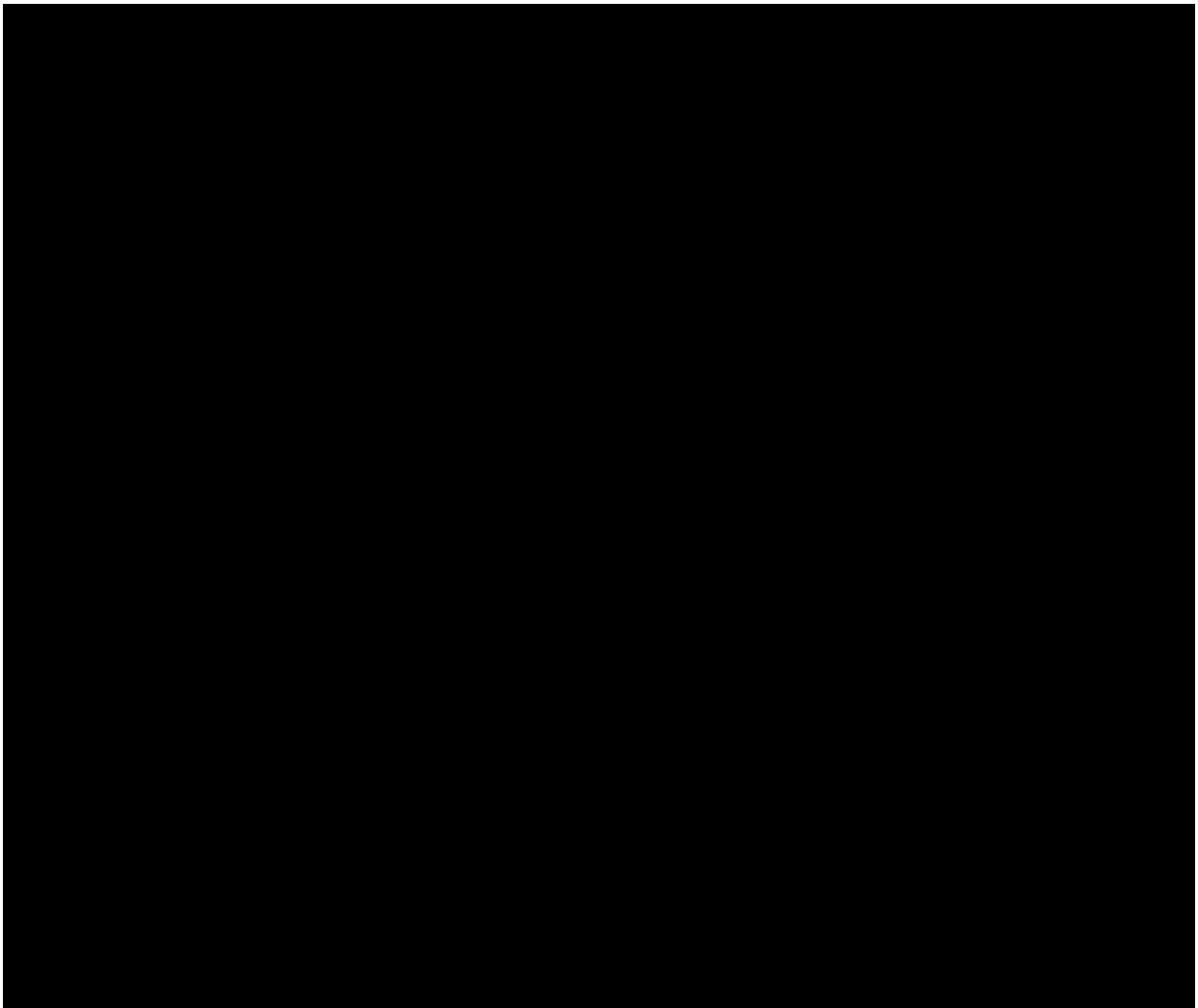
Any woman with a confirmed positive pregnancy test during screening is not eligible for randomization.

A positive urine pregnancy test during the treatment epoch of the study requires immediate interruption of study treatment until serum β -hCG is performed and found to be negative. If the serum β -hCG test is positive, study treatment must be definitively discontinued, as described in [Section 5.6.2](#).

6.5.7 Appropriateness of safety measurements

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





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 patient 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 Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
 - mild: usually transient in nature and generally not interfering with normal activities
 - moderate: sufficiently discomforting to interfere with normal activities
 - severe: prevents normal activities
- its relationship to the study treatment (suspected: no/yes),
- 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)
- 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 temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- 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; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

Worsening of psoriasis in this study is evaluated via the use of PASI, IGA mod 2011 [REDACTED] and is not expected to be captured as an AE in the eCRF. 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 2015). 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

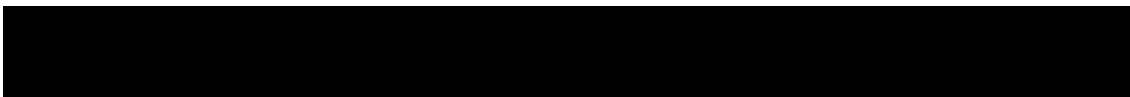
7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical condition(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
 - 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 (see Annex IV, ICH-E2D Guideline).



Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

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

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 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 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 AE 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 (*either initial or follow up information*) is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study treatment, complete the SAE Report Form in English, and submit it within 24 hours after awareness of the SAE to Novartis. Detailed instructions regarding the submission process and requirements for signature are listed in the investigator folder provided to each site. Follow-up information should be provided using SAE Report Form stating that this is a follow-up to a previously reported SAE.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the 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 with national regulatory requirements in participating countries.

7.3 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety DB irrespective of it being associated with an AE/SAE.

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

7.4 Pregnancy reporting

To ensure 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 CRFs with the investigators and their staff. During



the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice and the progress of enrollment. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight. The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on 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 CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

In addition, the unblinded field monitor will be responsible for monitoring unblinded activities performed by unblinded site personnel, including regular checks that the study treatment is being stored, prepared, dispensed and accounted for based on documentation filed that only unblinded personnel would have access to.

8.2 Data collection

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

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

8.3 Database management and quality control

Novartis staff [or CRO working on behalf of Novartis] review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query

Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the DB. The signed copy of the Data Query Form is kept at the investigator site.

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

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

ECGs will be read locally. Any clinically significant findings will be reported as (cardiovascular) medical history or AE depending upon timing of ECG assessment compared to screening.

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).

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 DB 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 DB after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

Not applicable.

8.5 Adjudication Committee

Not applicable.

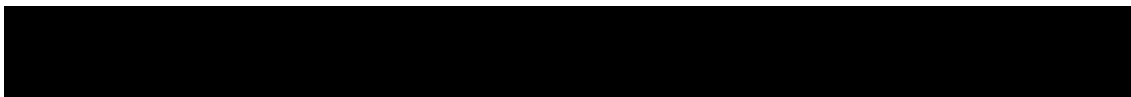
9 Data analysis

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, misrandomized subjects (misrandomized 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 analysed according to the treatment assigned at randomization.

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

For subject demographics and other baseline characteristics analyses will be based on the randomized set, unless otherwise specified.

Treatment groups for analyses for data will include:

- secukinumab
- ustekinumab

9.2 Subject 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.

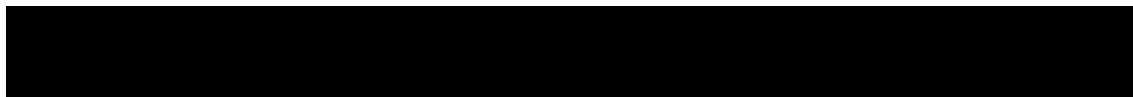
The number of active and placebo injections will be summarized by treatment group by means of contingency tables.

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 epoch.

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

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)

Details of the testing strategy are provided in [Section 9.4.2](#).

9.4.1 Variable(s)

Primary variable

The co-primary efficacy variables are PASI 90 response at Week 12 and IGA 0 or 1 response at Week 12. The analysis of the co-primary variables will be based on the FAS.

9.4.2 Statistical model, hypothesis, and method of analysis

Primary endpoint

The co-primary endpoints of this study are the proportion of subjects with PASI 90 response and IGA 0 or 1 response at Week 12 with secukinumab compared with ustekinumab.

The statistical hypothesis for PASI 90 response at Week 12 and IGA 0 or 1 response at Week 12 is that secukinumab is not superior to ustekinumab in the proportion of subjects with PASI 90 response and IGA 0 or 1 response at Week 12.

Let p_j denote the proportion of PASI 90 responders at Week 12 for treatment group j and r_j denote the proportion of IGA 0 or 1 responders at Week 12 for treatment group j , $j = 1, 0$, where

- 0 corresponds to ustekinumab
- 1 corresponds to secukinumab

The following hypothesis will be tested:

$$H_1: p_1 - p_0 \leq 0 \text{ versus } H_{A1}: p_1 - p_0 > 0,$$
$$H_2: r_1 - r_0 \leq 0 \text{ versus } H_{A2}: r_1 - r_0 > 0$$

In other words:

H_1 : Secukinumab is not superior to ustekinumab with respect to PASI 90 response at Week 12
 H_2 : Secukinumab is not superior to ustekinumab with respect to IGA 0 or 1 response at Week 12

The primary analysis method will be the logistic regression with treatment group; baseline bodyweight strata and baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons of secukinumab dose regimens versus ustekinumab 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.

The hypotheses H₁ and H₂ will both be tested at level 2.5% (one-sided), and significant results will only be achieved if both tests are rejected. i.e., if only one hypothesis is rejected and the other hypothesis is not rejected, superiority of secukinumab has not been demonstrated.

9.4.3 Handling of missing values/censoring/discontinuations

The following imputation methods will apply to the missing data:

- Response variables based on PASI score and IGA mod 2011 categories will be imputed with multiple imputations (MI) method as primary imputation method. 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.
- Non-responder imputation will be used as sensitivity method: Missing values with respect to response variables based on PASI score and IGA 2011 categories will be imputed with non-response regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues), exceptions will apply to the following:
 - If a subject dropped out of the study prior to last scheduled visit and being responders 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 for visit x, except for the missing data at last visit in the treatment period.

9.4.4 Sensitivity analyses

Sensitivity analyses will be performed as follows:

Co-primary variables and key secondary variables will be evaluated using the logistic regression as described in primary analysis method with non-responder imputations.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The key secondary endpoints of this study are planned as follow:



- speed of onset (PASI 75 at Week 4)
- PASI 75, PASI 90, PASI 100 and IGA 0/1 at Week 16
- PASI 75 and PASI 100 at Week 12
- PASI 90 at Week 52

Testing strategy

The following hypotheses will be tested sequentially and are included in the hierarchical testing strategy and type-I-errors will be set such that a family-wise type-I-error of $\alpha = 2.5\%$ (one-sided) is kept:

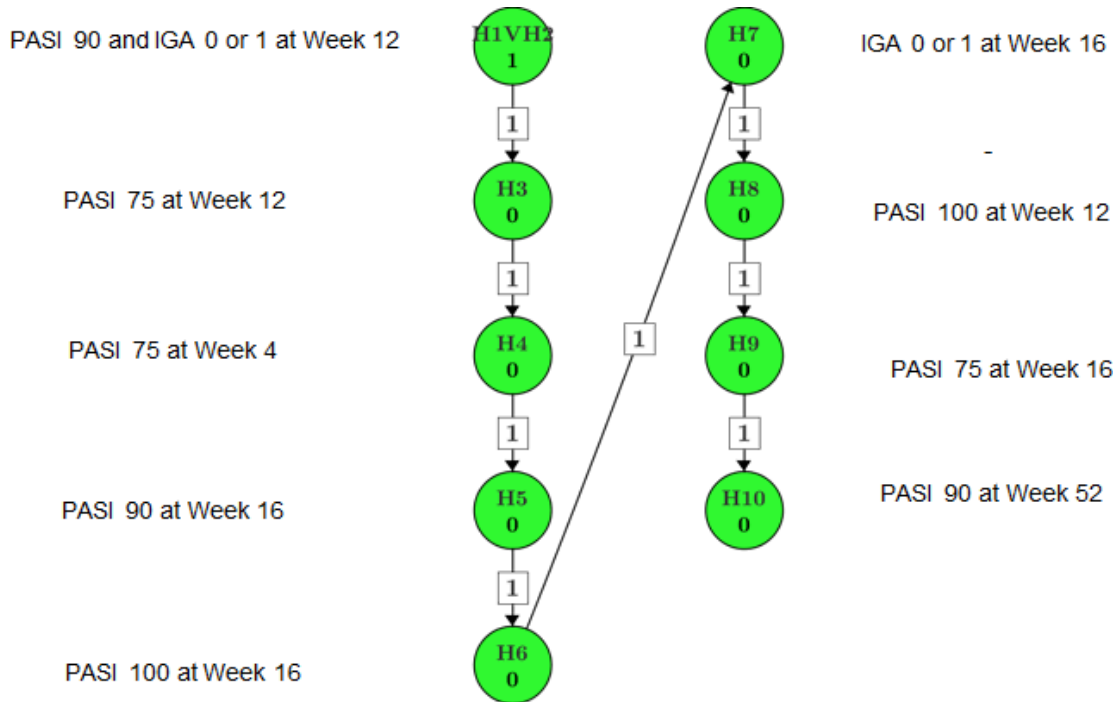
Co-primary objectives: H_1 to H_2 (see [Section 9.4.2](#))

Key secondary objectives:

- H_3 : secukinumab is not superior to ustekinumab with respect to PASI 75 response at Week 12
- H_4 : secukinumab is not superior to ustekinumab with respect to PASI 75 response at Week 4
- H_5 : secukinumab is not superior to ustekinumab with respect to PASI 90 response at Week 16
- H_6 : secukinumab is not superior to ustekinumab with respect to PASI 100 response at Week 16
- H_7 : secukinumab is not superior to ustekinumab with respect to IGA 0 or 1 response at Week 16
- H_8 : secukinumab is not superior to ustekinumab with respect to PASI 100 response at Week 12
- H_9 : secukinumab is not superior to ustekinumab with respect to PASI 75 response at Week 16
- H_{10} : secukinumab is not superior to ustekinumab with respect to PASI 90 response at Week 52

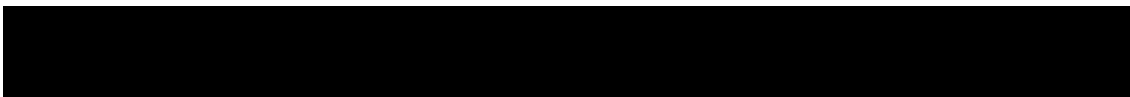
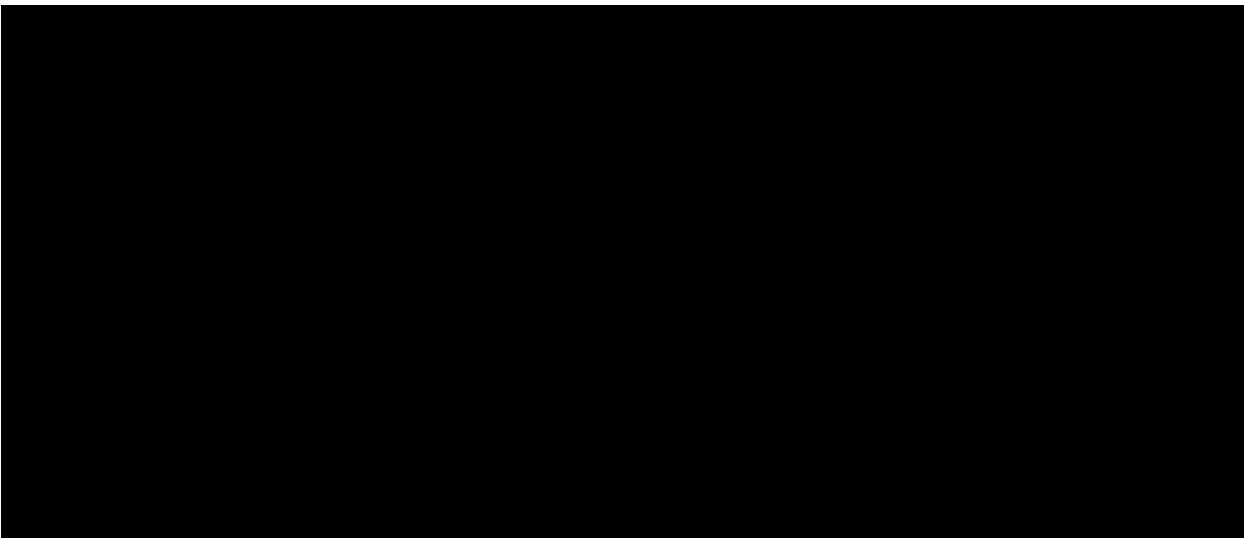
The graphical approach of ([Bretz et al. 2009](#)) for sequentially rejective testing procedures is used to illustrate the testing strategy:

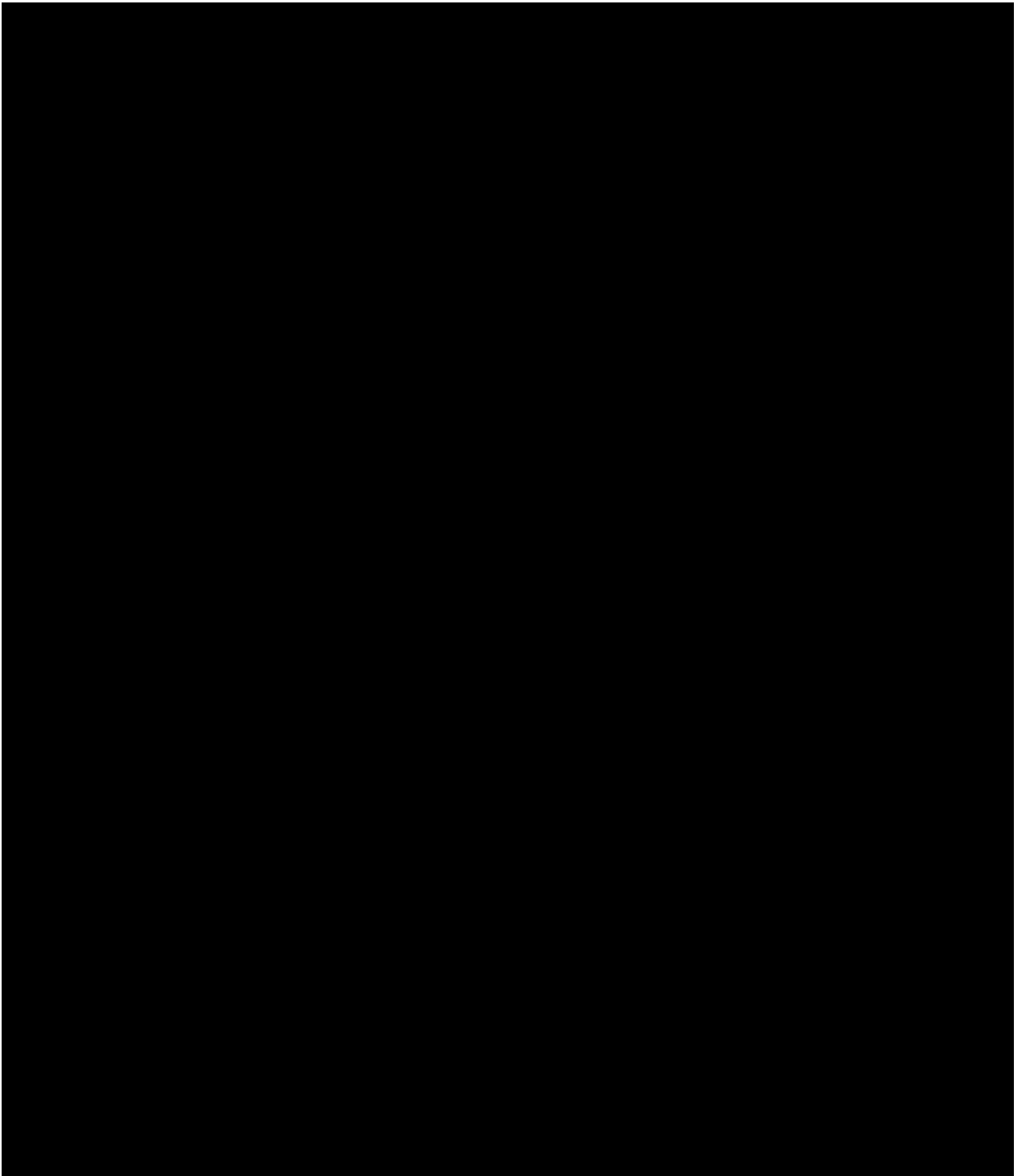




The efficacy variables involved in the above testing strategy will be analyzed analogously to the primary endpoints at Week 12. i.e., the logistic regression model with treatment group, baseline bodyweight strata and baseline PASI score [REDACTED]. Odds ratios will be computed for comparisons of secukinumab versus ustekinumab utilizing the logistic regression model fitted.

The testing sequence will continue to H₃ at α (one-sided) only if both H₁ and H₂ have been rejected at α (one-sided). Similarly, the testing sequence will continue to H₄ at α (one-sided) only if H₃ testing has been rejected. In case, H₉ has been rejected at α (one-sided), the corresponding alpha (α) will be passed to the next hypotheses corresponding H₁₀.





9.5.3 Safety variables

All safety evaluations will be performed on the Safety set.



Adverse events

Treatment emergent AEs (events started after the first dose of study treatment and within 84 days after the last study treatment, or events present prior to the first dose of study treatment but increased in severity based on preferred term within 84 days after the last study treatment) will be summarized. Only primary paths within MedDRA will be considered for AE reporting.

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

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

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

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

Laboratory data

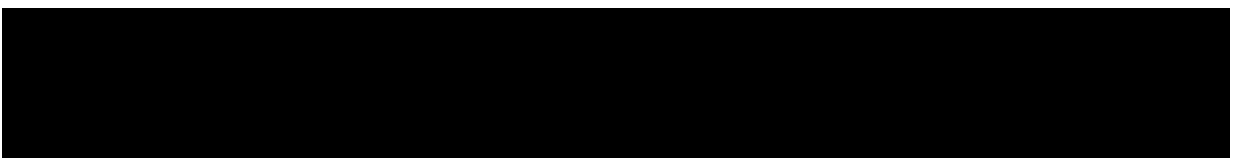
The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test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

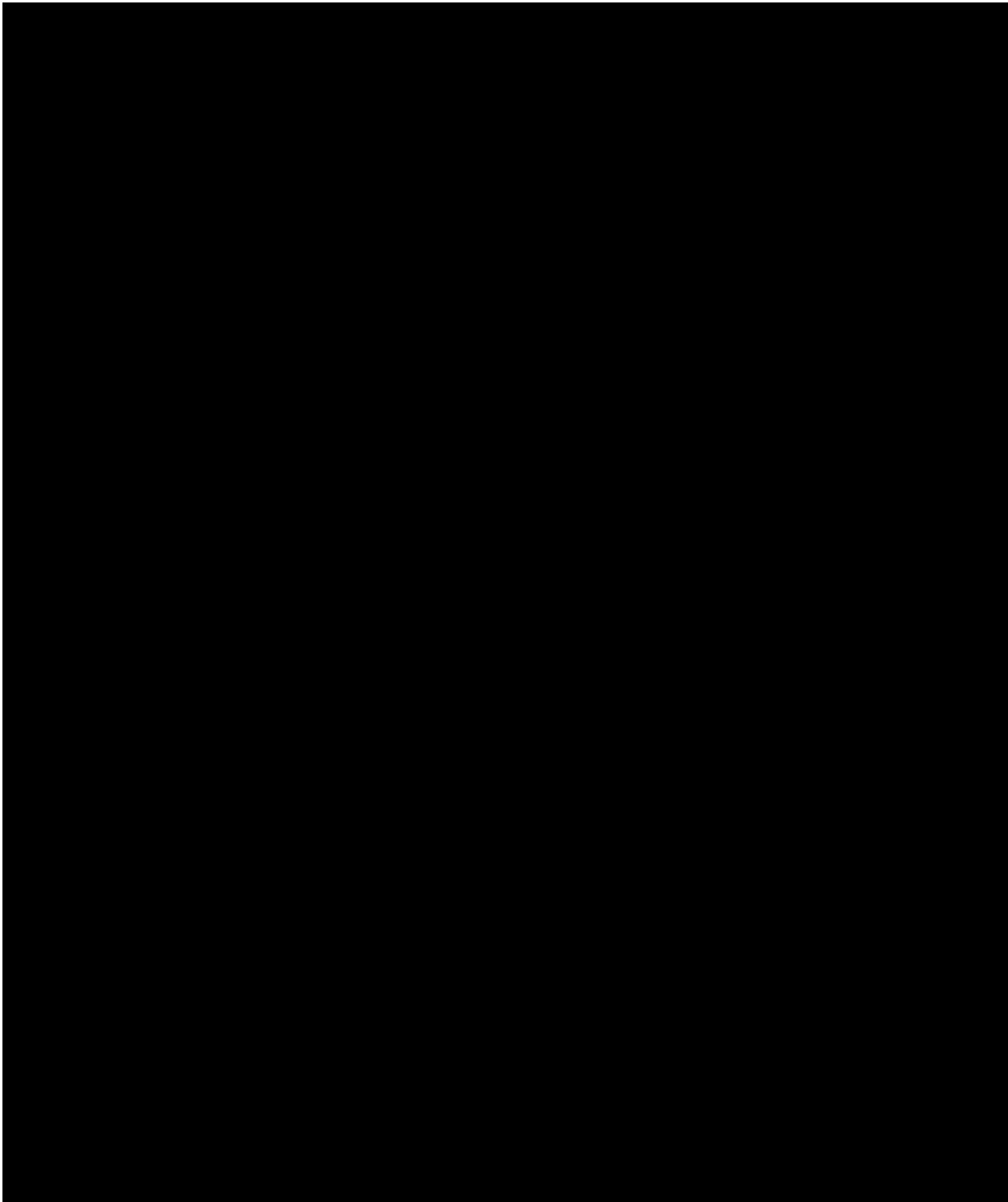
For each parameter, the maximum change from baseline within each study epoch will be analyzed analogously.

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

Vital signs

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





9.6 Interim analyses

Week 16 analysis will be performed after all subjects have completed Week 16 visit.

Additional analyses may be performed to support health authority interactions as necessary.



At the End of Study, a final analysis of all data collected up to last study visit (Week 52 or F8 as applicable) will be performed when all subjects have completed the last study visit.

9.7 Sample size calculation

The total sample size is 1100 subjects, i.e. using a balanced randomization 550 subjects will be randomized to each treatment group.

The secukinumab dose regimen versus ustekinumab with respect to the co-primary endpoint PASI 90 and IGA 0/1 at Week 12 are tested at $\alpha=2.5\%$ (one-sided). The response rates are computed based on CLEAR (CAIN457A2317) study data. The assumed response rates and power are shown in [Table 9-1](#). The power calculations are based on chi-square test (nQuery Advisor 7.0, two group chi-square test of equal proportions).

Table 9-1 Power to show superiority of secukinumab versus ustekinumab for co-primary endpoints

Endpoints	Secukinumab 300 mg Response (%)	Ustekinumab Response (%)	Power
PASI 90 at Week 12	66%	52%	>99%
IGA 0/1 at Week 12	77%	64%	>99%

Note: one-sided type-I-error=2.5%, N=550 per group

If the assumed PASI 90 response rate at week 12 for secukinumab is 66% and for ustekinumab is 52%, the power to reject the corresponding null hypothesis is greater than 99%. Similarly, if the assumed IGA 0/1 response rate at week 12 for secukinumab is 77% and for ustekinumab is 64%, the power to reject the corresponding null hypothesis is also greater than 99%. Details for other key secondary endpoints are provided in [Table 9-2](#).

9.8 Power for analysis of key secondary variables

The secukinumab dose regimen versus ustekinumab with respect to the key secondary endpoints are tested at $\alpha=2.5\%$ (one-sided). The response rates are computed based on unpublished CLEAR (CAIN457A2317) study data.

Table 9-2 Power to show superiority of secukinumab versus ustekinumab for key secondary endpoints

Endpoints	Secukinumab 300 mg Response (%)	Ustekinumab Response (%)	Power
PASI 75 at Week 12	88%	79%	97%
PASI 75 at Week 4	47%	21%	>99%
PASI 90 at Week 16	74%	55%	>99%
PASI 100 at Week 16	40%	24%	>99%
IGA 0/1 at Week 16	80%	65%	>99%
PASI 100 at Week 12	34%	23.5%	96%

Endpoints	Secukinumab 300 mg Response (%)	Ustekinumab Response (%)	Power
PASI 75 at Week 16	90%	82%	96%
PASI 90 at Week 52	70%	60.5%	90%

Note: one-sided type-I-error=2.5%, N=550 per group

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the subject. In cases where the subject's representative gives consent, the subject 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 childbearing 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.

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



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13 Appendix 1: Clinically notable laboratory values and vital signs

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

No specific action is pre-defined within this protocol to respond to specific abnormal laboratory values as it will be decided by the investigator/qualified site staff 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

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

Renal Function

- Creatinine (serum): > 1.5 x ULN

Hematology Variables

- Hemoglobin: ≥ 20 g/L 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