NOVARTIS

Global Clinical Development - General Medicine

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457A2318 / NCT03066609

A randomized, double-blind, placebo controlled, multicenter study of subcutaneous secukinumab, to demonstrate efficacy after twelve weeks of treatment and to assess safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis with or without psoriatic arthritis comorbidity

Document type:	Amended Clinical Trial Protocol
EUDRACT number:	2016-000524-25
Version number:	v01 Clean
Clinical trial phase:	III
Release date:	09-June-2017

Clinical Trial Protocol Template Version 03 (August 2015)

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

[redacted]

List of tables

List of figures

[redacted]

List of abbreviations

AE	Adverse Event
AI	Auto-injector
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CFR	US Code of Federal Regulations
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CS	Corticosteroids
CRO	Contract Research Organization
CTC	Common Terminology Criteria
[redacted]	[redacted]
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
e.g.	example
EU	European Union
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire© – Disability Index
GGT	Gamma –glutamyl transferase
hCG	Human chorionic gonadotropin
hsCRP	high sensitivity C-reactive protein
HIV	Human Immunodeficiency virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed Consent Form
IEC	Independent Ethics Committee
[redacted]	[redacted]
IGA mod 2011	Investigator's Global Assessment modified 2011
IL	interleukin
IN	Investigator Notification
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LYO	lyophilized powder
MedDRA	Medical dictionary for regulatory activities
OC/RDC	Oracle Clinical/Remote Data Capture
PASI	Psoriasis Area and Severity Index
PFS	Pre-filled syringe
PhGA	physician global assessment
PtGA	patient's global assessment

[redacted]

[redacted]	[redacted]
PRO	Patient Reported Outcome
PUVA	Photochemotherapy (e.g. psoralen + UVA treatment)
QFT	QuantiFERON TB-Gold test
SAE	Serious Adverse Event
s.c.	Subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	tuberculosis
TBL	Total Bilirubin
TCS	Topical Corticosteroid
Th17	T helper 17 cells
TNF	Tumor necrosis factor
UV	Ultraviolet
UVA	Ultraviolet A, long wave 400 nm–315 nm
UVB	Ultraviolet B, medium wave 315 nm–280 nm
WBC	White blood cells / leukocytes
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient 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 patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 01

Amendment rationale

The aim of this amendment is to introduce a provision for a Week 16 analysis. This analysis will include primary endpoint data at Week 12 and in addition data at Week 16 visit.

[redacted]

This amendment also introduces the provision for additional subsequent interim analyses that may be conducted to fulfill any request from Health Authorities.

At the time of this amendment release, the enrollment into the study is ongoing.

In addition, this amendment is used to clarify minor inconsistencies between various protocol sections, and correct minor errors; these do not affect the study design or population.

Changes to the protocol

The major changes made to the protocol are listed below:

- Section 3.5 Purpose and timing of interim analyses/design adaptations
  Amended to introduce a Week 16 analysis and the provision for additional subsequent interim analyses that may be conducted to fulfill any HA requests

- Section 5.3 Treatment blinding
  Updated to introduce unblinding of designated Novartis personnel who may be involved in the Week 16 analysis and additional subsequent interim analyses that may be conducted to fulfill any HA requests

- Section 5.5.3 Instructions for prescribing and taking study medication
  Clarification regarding order of assessments prior to injection of study treatment

- Section 9 Data analysis
  Amended to include Week 16 visit analysis and the provision for additional subsequent interim analyses that may be conducted to fulfill any HA requests

- Section 9.7 Interim analyses
  Amended to include Week 16 visit analysis and the provision for additional subsequent interim analyses that may be conducted to fulfill any HA requests.

This protocol amendment also includes corrections of minor errors/inconsistencies across sections of the protocol and changes to align with the study design and increase clarity of the text.

[redacted]

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

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC and HA approval where needed and according to local regulations, prior to implementation. The changes herein do NOT affect the trial specific model ICF.

Protocol summary

Protocol number	AIN457A2318
Title	A randomized, double-blind, placebo controlled, multicenter study of subcutaneous secukinumab, to demonstrate efficacy after twelve weeks of treatment and to assess safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis with or without psoriatic arthritis comorbidity
Brief title	Study of efficacy and safety of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis
Sponsor and Clinical Phase	Novartis / Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to demonstrate superiority of secukinumab at Week 12 in subjects with moderate to severe chronic plaque-type psoriasis in terms of both PASI 75 and IGA mod 2011 0 or 1 response, compared to placebo, and to assess the maintenance of efficacy of secukinumab until Week 52. In addition, the study will assess efficacy of secukinumab compared to placebo in treating subjects with psoriatic arthritis comorbidity in terms of ACR 20/50/70 response and ACR components at Week 12 and over time until Week 52. The study will also assess the safety and tolerability of secukinumab with prefilled syringe in the patient population over the study period.
Primary Objective(s)	To demonstrate the superiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis in terms of both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo.
Secondary Objectives	• To demonstrate the superiority of secukinumab in terms of PASI 90 response at Week 12 compared to placebo. • To assess the efficacy of secukinumab in maintaining PASI 75 response at Week 52 in subjects who were PASI 75 responders at Week 12 or IGA mod 2011 0 or 1 response at Week 52 in subjects who were IGA mod 2011 0 or 1 responders at Week 12. • To assess the efficacy of secukinumab in terms of PASI score, IGA

	mod 2011 score, PASI 50/75/90/100 and IGA mod 2011 0 or 1 response over time up to Week 12 compared to placebo and over time up to Week 52 • To assess the efficacy of secukinumab in terms of time to PASI 75 response up to Week 12 compared to placebo. • To investigate the clinical safety and tolerability of secukinumab, as assessed by vital signs, clinical laboratory variables, ECG and adverse events monitoring compared to placebo. • To assess the efficacy of secukinumab in treating psoriatic arthritis in subjects with this comorbidity at Baseline in terms of American College of Rheumatology (ACR) 20/50/70 response over time up to Week 52.
Study design	This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in approximately 536 subjects with moderate to severe chronic plaque-type psoriasis with or without psoriatic arthritis comorbidity. It is expected that subjects will be enrolled at around 45 study sites in China and other countries Randomization will be stratified by geographical region and presence of psoriatic arthritis at Baseline. Subjects will be randomized using a 2:1:1 ratio into one of the treatment groups: secukinumab 300 mg s.c., secukinumab 150 mg s.c., and placebo s.c.
Population	The study population will consist of a representative group of male and female adult out-patients with moderate to severe chronic plaque-type psoriasis, poorly controlled by topical treatments and/or phototherapy and/or previous systemic therapy. As this study may be used to support the registration of secukinumab in China, the majority of the patients will be enrolled in China, for example approximately 80% from China and the rest from other countries.
Key Inclusion criteria	1. Subjects must be able to understand and communicate with the investigator and comply with the requirements of the study 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 at least 18 years of age at time of screening. 3. Chronic plaque-type psoriasis present for at least 6 months and diagnosed before Baseline. 4. Moderate to severe psoriasis as defined at Baseline by: • PASI score of 12 or greater, and • IGA mod 2011 score of 3 or greater (based on a static scale of 0 – 4), and • Body Surface Area (BSA) affected by plaque-type psoriasis of 10% or greater. 5. Candidate for systemic therapy. This is defined as a subject having moderate to severe chronic plaque-type psoriasis that is inadequately controlled by • topical treatment and/or, • phototherapy and/or, • previous systemic therapy.

Key Exclusion criteria	1. Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis) at Screening or Baseline. 2. Drug-induced psoriasis. 3. Ongoing use of prohibited treatments. 4. Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor. 5. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations. 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 hCG laboratory test.
Study treatment	• Investigational therapy: secukinumab 150 mg and 300 mg s.c • Reference therapy: placebo s.c.
Efficacy assessments	• Investigator's Global Assessment for psoriasis (IGA mod 2011; scale from 0 – 4) • Psoriasis Area and Severity Index (PASI; score from 0 – 72) • ACR response
Key safety assessments	• Evaluation of all AEs and SAEs including injection site reactions, hypersensitivity reactions and occurrence of infections. • Physical examination • Vital signs • Weight • Laboratory evaluations (Hematology, Clinical chemistry) • Urinalysis • ECG • [redacted]
Other assessments	• Clinician Reported Outcomes • Patient Reported Outcomes • [redacted]
Data analysis	The primary endpoint (PASI 75 and IGA mod 2011 0 or 1 response at Week 12) will be evaluated using an exact logistic regression model with treatment group, baseline body weight, geographical region, presence of psoriatic arthritis, and baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons of secukinumab dose regimens versus placebo utilizing the exact logistic regression model fitted. In case of rates of 0% or 100% in one of the treatment groups, Fisher's exact test will be applied.
Key words	psoriasis, PASI, IGA mod 2011, psoriatic arthritis, secukinumab

[redacted]

1 Introduction

1.1 Background

Psoriasis is a chronic, relapsing, immune mediated multi-system disorder primarily affecting the dermis and epidermis. Skin lesions are classified as erythemato-squamous, which indicates that both the vasculature (erythema) and the epidermis (increased scale formation) are involved. The prevalence of psoriasis in different populations can vary between 0 and 12% (Schon and Boehncke 2005), with estimates of 2.8% in western populations (Naldi 2004; Farber 1998) and 0.47% in China (Ding 2012).

Plaque psoriasis (also called plaque-type or chronic plaque) is the most frequent clinical presentation, also called psoriasis vulgaris. The erythematous plaques are well defined with sharp borders. The silvery grey scale on the surface of the lesions is easily removed. Sharply demarcated lesions can present on the extensor surfaces of the knees and elbows and on the trunk. Lesions are often symmetrically distributed. The size of the lesions is highly variable. Psoriasis may also occur on the scalp, palms and/or soles (palmoplantar psoriasis), nails and in skin folds (intertrigo psoriasis).

The etiology of psoriasis is unknown. Accumulating evidence indicates that psoriasis is a multifactorial disorder caused by the concerted action of multiple disease genes in a single individual, triggered by environmental factors. Genetic factors influence the pattern of psoriasis, severity and the age of onset (Griffiths and Barker 2007). In recent years, increased attention has been paid to comorbidities of psoriasis. A distinct pattern of chronic disorders was found to be significantly associated with psoriasis, including arterial hypertension, hyperlipidemia, and coronary heart disease. Psoriatic arthritis (PsA) is a particular instance of comorbidity in psoriasis. This chronic, immune-mediated inflammatory disease encompasses a spectrum of overlapping clinical entities (Moll and Wright 1973) belonging to a group of conditions referred to as seronegative spondylarthropathies (SpA) and possibly mediated via a common pathway including the IL-23/IL-17 axis. The prevalence varies from 20–420 per 100,000 population across the world (Dhir et al 2013) with the limited data from Asia (Alamanos Y et al 2008). Based on the population-based surveys in China, the prevalence of PsA appeared to be similar to the rest of the world, ranging from 10 to 100 per 100,000 population (Zeng QY et al 2008). However, among the Japanese population, there is a 64- and 180-fold lower incidence with prevalence between 0.1 and 1 per 100,000 population as compared with the median incidence and prevalence of all other studies (Hukuda S et al 2001, Dhir et al 2013). In addition, a multi-ethnic study reported that PsA was significantly more common among the Indian population than the ethnic distribution of the Singapore population (Thumboo J et al 1997).

Other reports refer to prevalence of PsA between 6% and 42% in psoriatic patients in Europe, USA and South Africa (Gladman et al 2005). However, the overall numbers are lower in Asian countries. PsA was observed in 9% of the patients with psoriasis in Iran (Jamshidi F et al 2008), Korea (Baek HJ et al 2000), and India (Prasad PV et al 2007); 5% in China (Fan X et al 2007); 2% in Turkey (Kundakci N et al 2002), and 1% in Japan (Kawada A et al 2003). Also, a study conducted in Singapore reported that the Indian population with psoriasis had twice the risk of developing PsA when compared with the Chinese population (Thumboo J et al 1997) with the amplitude of variations possibly reflecting differences in diagnostic

[redacted]

complexities and ethnicities difference. Psoriatic arthritis is associated with significant morbidity and disability and thus, it constitutes a major socioeconomic burden.

Once psoriasis appears as a localized disease, it persists throughout life, manifesting itself at unpredictable intervals. Spontaneous remissions of varying duration do occur with varying frequencies. Data relative to permanent remissions, either spontaneous or induced, appears to be unavailable in the literature.

Therefore, psoriasis represents a lifelong condition for the patient. A study reported reduction in physical functioning and mental functioning comparable to that seen in cancer, arthritis, hypertension, heart disease, diabetes and depression (Rapp et al 1999).

The patient and his or her family must learn to deal with the illness and its treatment in such a manner as to reduce the potential negative influence on self-esteem. Both the appearance of the affected areas and the chronic nature of the disease impose a heavy psychological burden. In addition to dermatological care, attention must be given to the emotional problems that may be created in the patient and the family (Christophers and Mrowietz 2003; de Waardvan der Spek and Oranje 2006).

Secukinumab (AIN457) is a recombinant high-affinity fully human monoclonal anti-human Interleukin-17A antibody of the IgG1/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 several autoimmune and inflammatory processes. IL-17A is mainly produced by memory effector CD4+ and CD8+ T lymphocytes. IL-17A 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 symptoms.

To confirm the findings of basic research and early clinical studies regarding the crucial role of interleukin-17A in psoriasis, 2 randomized, phase 3 trials were conducted to assess the efficacy and safety of secukinumab, at a dose of 300 mg or 150 mg, administered as induction therapy (with assessment at Week 12) and maintenance therapy (with assessment at week 52) in patients with moderate-to-severe plaque psoriasis. The CAIN457A2302/ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) study compared secukinumab with placebo, and the CAIN457A2303/FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis) study compared secukinumab with placebo and etanercept, the first tumor necrosis factor (TNF) inhibitor approved by the Food and Drug Administration for moderate-to-severe plaque psoriasis. The studies evaluating pre-filled syringe (PFS) and auto-injector (AI) forms of secukinumab administration (Studies CAIN457A2308 and CAIN457A2309) showed no new or unexpected administration and immune reactions compared to the profile seen in studies using lyophilized powder (LYO) (e.g., Studies CAIN457A2302 and CAIN457A2303).

The results of these phase 3 studies validate interleukin-17A as an important therapeutic target in moderate-to-severe plaque psoriasis, confirming earlier findings from basic research and phase 2 trials of secukinumab that suggested that interleukin-17A plays a role in the pathogenesis of psoriasis. The superiority of secukinumab over these comparators (both placebo and etanercept) was shown in both studies. Secukinumab was associated with a rapid

[redacted]

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 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 the superior efficacy of secukinumab over the TNF inhibitor etanercept over a period of 52 weeks, a duration that exceeds the 12-week study duration in a previous phase 3, blinded, direct comparison of two biologic therapies for psoriasis. 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 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 results of a proof-of-concept study in patients with moderate to severe psoriatic arthritis (CAIN457A2206) suggest that secukinumab was well tolerated and demonstrated preliminary evidence for therapeutic benefit. ACR response rates under secukinumab and placebo did not differ significantly at week 6, however the onset of secukinumab action was more rapid, with ACR20 and ACR50 responses occurring as early as two weeks after the beginning of therapy and numerically greater reductions in ACR20, ACR50 and ACR70 responses under secukinumab compared to placebo at almost every time point up to week 24. Acute phase reactant CRP was reduced at week 6 of the treatment. Also, the data that is available from the ongoing phase 3 FUTURE 2 study suggests that secukinumab can improve the signs and symptoms in patients with psoriatic arthritis. All studied doses 75 mg, 150 mg and 300 mg s.c. showed significantly higher ACR 20 response rates at Week 24 (29.3%, 51% and 54% respectively) compared to placebo (15.3%) (McInnes et al 2015).

As of 25 June 2015, approximately 12,000 subjects (healthy subjects and patients) have been enrolled in Novartis sponsored clinical studies with secukinumab, with over 9,600 subjects having received secukinumab treatment at doses ranging from 0.1 mg/kg to 30 mg/kg intravenously (i.v.), and from 25 mg to 300 mg subcutaneously (s.c.), given as single or multiple doses. As of 25 July 2015, there are 79 completed and multiple ongoing trials conducted with secukinumab in indications including psoriasis, psoriatic arthritis, uveitis, multiple sclerosis, rheumatoid arthritis, rheumatic polymyalgia, type I diabetes mellitus, asthma, and ankylosing spondylitis. Full safety results including all reported AEs are currently available for completed studies across different indications. The Investigator's Brochure (IB) provides a more detailed review of the pre-clinical and clinical information on secukinumab.

Results are available from a bioequivalence study (CAIN457A2106) in which the pharmacokinetics, safety and tolerability of a pre-filled syringe (test) and the lyophilisate formulation (reference) were compared. Secukinumab (reference, 300 mg or test, 300 mg) was subcutaneously injected (2x 1 mL) to the abdominal region of 150 healthy volunteers in a randomized, open label, single dose, and parallel group study. Serum concentrations were measured up to 112 days post dose by ELISA. The primary outcome was assessed via geometric mean ratios of the log-transformed Cmax, AUClast and AUCinf as PK parameters. The geometric mean ratios (90% CIs) of the test to reference formulation for Cmax, AUClast

[redacted]

and AUCinf were 1.04 (0.96-1.12), 1.01 (0.93-1.08) and 1.00 (0.92-1.08), respectively. The confidence intervals were entirely within the 0.8-1.25 boundaries and therefore, the prefilled syringe met the standard criteria for assuming bioequivalence. Further, phase III data with the liquid formulation are now available that demonstrate the safe and effective use of both liquid forms i.e. prefilled syringe (Study A2308) and autoinjector (Study A2309).

In addition, pooled data from two phase III studies (Study A2302 and A2303) presented analysis of 443 Asian subjects with moderate to severe plaque psoriasis. Similar to the overall population, PASI 75 responses in Asian subjects were significantly higher in secukinumab 300mg (74.4%) and 150mg (67.5%) treatment arms compared with placebo (6.8%; $p < 0001$, both doses) or etanercept treatment (27.4%; $p < 0001$, both doses) at Week 12. Also, IGA 0/1 after 12 weeks was significantly higher in secukinumab 300 and 150mg groups (52.8% and 46.0% respectively) compared with 2.6% in placebo group ($p < 0001$, both secukinumab doses) or 17.8% in the etanercept treatment arm ($p < 0001$ for both secukinumab doses). Moreover, PASI 90 responses were also significantly higher in the secukinumab 300 mg (53.6%) and 150 mg (40.5%) arms when compared with placebo (0.9%) or etanercept (13.7%) treatment at week 12. In addition, PASI 75 and PASI 90 responses were consistently higher in the 300 mg group when compared with the 150 mg group. Clinical responses to secukinumab were increased at Week 16 and sustained after Week 52. The most common AEs with either secukinumab dose were infections and infestations, including nasopharyngitis. In summary, in this 52 weeks pooled analysis, secukinumab demonstrated consistent efficacy and safety profile that is comparable to the overall population in the phase III studies.

1.2 Purpose

The purpose of this study is to demonstrate superiority of secukinumab at Week 12 in subjects with moderate to severe chronic plaque-type psoriasis in terms of both PASI 75 and IGA mod 2011 0 or 1 response, compared to placebo, and to assess the maintenance of efficacy of secukinumab until Week 52. In addition, the study will assess efficacy of secukinumab in treating subjects with psoriatic arthritis comorbidity in terms of ACR 20/50/70 response and ACR components at Week 12 compared to placebo and over time until Week 52. The study will also assess the safety and tolerability of secukinumab with prefilled syringe in the patient population over the study period. Efficacy and safety data from this global study will primarily be used to support the registration of secukinumab in China, for the treatment of moderate to severe chronic plaque-type psoriasis and psoriatic arthritis comorbidity.

2 Study objectives and endpoints

2.1 Primary objective

To demonstrate the superiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis in terms of both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo.

2.2 Secondary objectives

- To demonstrate the superiority of secukinumab in terms of PASI 90 response at Week 12 compared to placebo.

[redacted]

- To assess the efficacy of secukinumab in maintaining PASI 75 response at Week 52 in subjects who were PASI 75 responders at Week 12 or IGA mod 2011 0 or 1 response at Week 52 in subjects who were IGA mod 2011 0 or 1 responders at Week 12.
- To assess the efficacy of secukinumab in terms of PASI score, IGA mod 2011 score, PASI 50/75/90/100 and IGA mod 2011 0 or 1 response over time up to Week 12 compared to placebo and over time up to Week 52.
- To assess the efficacy of secukinumab in terms of time to PASI 75 response up to Week 12 compared to placebo.
- To investigate the clinical safety and tolerability of secukinumab, as assessed by vital signs, clinical laboratory variables, ECG and adverse events monitoring compared to placebo.
- To assess the efficacy of secukinumab in treating psoriatic arthritis in subjects with this comorbidity at Baseline in terms of American College of Rheumatology (ACR) 20/50/70 response over time up to Week 52.

[redacted]

3 Investigational plan

3.1 Study design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in approximately 536 subjects with moderate to severe chronic plaque-type psoriasis with or without psoriatic arthritis comorbidity. It is expected that subjects will be enrolled at around 45 study sites in China and other countries.

The study consists of four epochs: Screening (of at least 1 week and up to 4 weeks), Induction (of 12 weeks), Maintenance (of 40 weeks), and Follow-up epoch (of 8 weeks). An outline of the study is presented in Figure 3-1 and a detailed visit and assessment schedule is presented in Table 6-1.

Safety, efficacy [redacted] will be performed according to the schedule presented in Table 6-1.

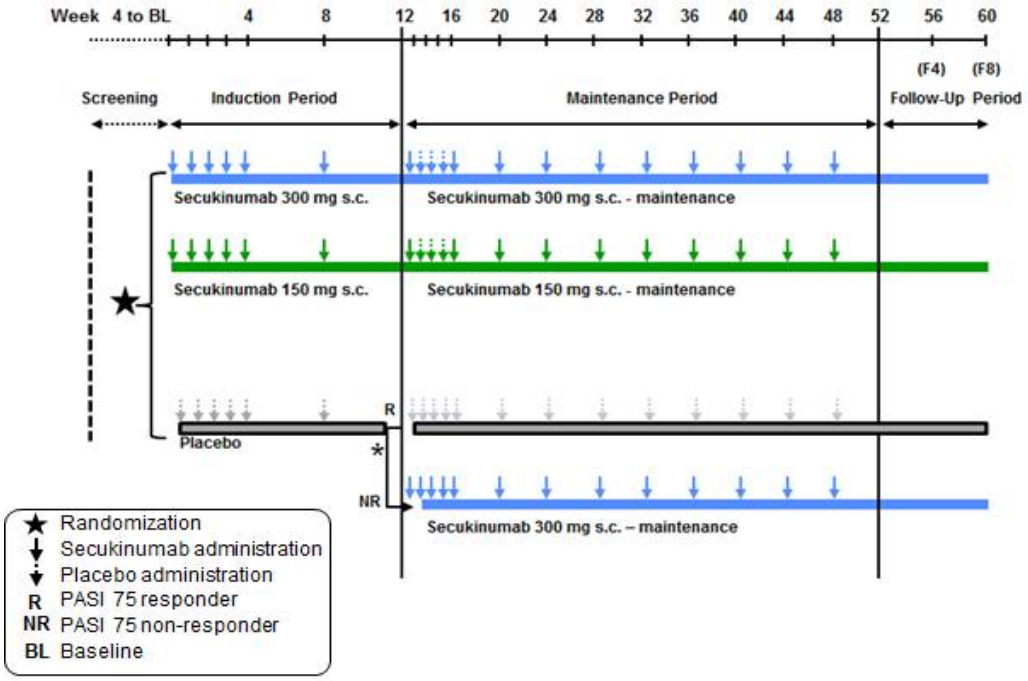
[redacted]

Randomization will be stratified by geographical region and presence of psoriatic arthritis at Baseline. Subjects will be randomized using a 2:1:1 ratio into one of the treatment groups below:

- **Secukinumab 300 mg regimen group:** secukinumab 300 mg s.c. (two injections of secukinumab 150 mg dose) once weekly for four weeks (at Baseline, Weeks 1, 2, and 3), followed by dosing every four weeks, starting at Week 4 and until Week 48, except for Weeks 13, 14, and 15 where they will receive a weekly dose of placebo (two injections per dose) to maintain the blind.
- **Secukinumab 150 mg regimen group:** secukinumab 150 mg (one injection of secukinumab 150 mg and one placebo secukinumab injection) once weekly for four weeks (at Baseline, Weeks 1, 2, and 3), followed by dosing every four weeks, starting at Week 4 and until Week 48, except for Weeks 13, 14, and 15 where they will receive a weekly dose of placebo (two injections per dose) to maintain the blind.
- **Placebo group:** placebo secukinumab (two placebo injections per dose) once per week for four weeks (at Baseline, Weeks 1, 2, and 3), followed by dosing every four weeks (Weeks 4 and 8). Prior to receiving the Week 12 dose, all subjects in the placebo group will be assigned to the following treatment groups based on PASI 75 response status at Week 12, as follows:
  - **PASI 75 responders** (per definition in Section 6.4.2) will continue on placebo and will receive their placebo injections on Weeks 12, 13, 14, 15, and then every four weeks starting at Week 16 until Week 48.
  - **PASI 75 non-responders** (per definition in Section 6.4.2) will be reassigned to 300 mg secukinumab regimen group and receive their treatment on Weeks 12, 13, 14, 15 and then every four weeks starting at Week 16 until Week 48.

[redacted]

Figure 3-1 Study design



Screening (Screening to Baseline)

The screening epoch of at least 1 week and up to 4 weeks will be used to assess eligibility of the subjects and to taper subjects off disallowed medications.

Induction epoch (Baseline to Week 12 pre-dose)

The Induction epoch is defined as Baseline through Week 12 (prior to Week 12 dose). At the start of the Induction epoch, eligible subjects will be randomized in a 2:1:1 ratio into one of three treatment groups (secukinumab 300 mg, secukinumab 150 mg or placebo group respectively). During the Induction epoch, subjects will be visiting the study site at Baseline and Weeks 1, 2, 3, 4, 8 and 12.

During the Induction epoch, all three treatment groups will receive study treatment and/or placebo weekly for four weeks (Baseline and Weeks 1, 2 and 3) and then one dose of study treatment and/or placebo at Weeks 4 and 8 (last dose during the Induction epoch).

Assessments for the primary endpoint will be performed at Week 12 for all treatment arms **prior to** the dose at Week 12.

In addition, for subjects who discontinue study treatment prematurely for any reason before the end of the induction epoch, visit Week 12 (planned End of Induction Epoch (EOI)) should be performed approximately four weeks after their last dose of study treatment (secukinumab or placebo) and then the subject should enter the follow-up epoch.

Maintenance epoch (Week 12 dosing to Week 52)

The Maintenance epoch is defined from dosing at Week 12 (first dose of the Maintenance epoch) through Week 52. At Week 12, non-responders of the induction placebo treatment group will be reassigned to 300 mg secukinumab, as described above. Initially they will receive an active loading regimen with 5 weekly doses, identical to the induction epoch for those subjects who were initially randomized to receive secukinumab. To ensure a double-blind design, all subjects in the other treatment arms will receive as well 5 weekly doses starting Week 12 up to Week 16, that will either be active or placebo doses, depending on their 4-weekly treatment schedule (150 mg or 300 mg secukinumab groups will receive 4-weekly active treatment at Week 12 and Week 16, and placebo treatment at Week 13, 14 and 15 and placebo PASI 75 responders will receive only placebo). The dose given at Week 12 is the first dose of the maintenance epoch and is followed by doses of secukinumab study treatment and / or placebo weekly up to Week 16, as described above, and every four weeks up to Week 48 for all treatment arms. The Week 52 Visit is the end of maintenance visit (EOM).

Subjects who complete the maintenance treatment epoch will enter the post-treatment follow-up epoch or join a possible extension study, if available.

In addition, for subjects who discontinue study treatment prematurely for any reason before the end of the maintenance epoch, visit Week 52 (planned End of Maintenance Epoch (EOM) visit) should be performed approximately four weeks after their last dose of study treatment (secukinumab or placebo) and then the subject should enter the follow-up epoch.

Follow-up epoch (Week 52 to Week 60)

Subjects who discontinue the study prematurely for any reason will have EOI/EOM visits, approximately 4 weeks after receiving the last dose of study treatment and should enter the follow up epoch.

The treatment-free follow-up visits (no study treatment administered during follow-up epoch) will be at Week 56 (Follow-up visit F4, which is 4 weeks after the EOM visit but 8 weeks post last dose of secukinumab or placebo secukinumab) and Week 60 (Follow-up visit F8 (or End of Follow-up (EOF)), which is 8 weeks after the EOM visit but 12 weeks post last dose of secukinumab or placebo.

3.2 Rationale for study design

The double-blind, randomized, parallel-group, placebo-controlled design used in this study is aligned with similar phase III trials of other systemic therapies for psoriasis and psoriatic arthritis including biologics and immunomodulatory drugs, and complies with guidelines and feedback of the Health Authorities, including the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Pharmaceuticals, Medical Devices Agency of Japan (PMDA) and CFDA requirement in use of biologic drug. Primary endpoint of the trial is assessed after 12 weeks, allowing for comparisons of efficacy at a point in time which is common to all currently approved/available systemic therapies of psoriasis. The total study duration, including one year of treatment plus the follow-up period, will allow for the assessment of long term safety and efficacy. Blinding is maintained beyond the primary endpoint, to ensure reliable efficacy measures beyond the induction period of 12 weeks.

[redacted]

Regular assessments of disease activity and clinical status ensure close monitoring of subject safety and give steady occasions to both the subjects and the investigators to decide if continuous participation in the study does benefit the subjects.

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

The proposal to use doses of 300 mg and 150 mg s.c. administered with a loading regimen for induction, and treatment every four weeks for maintenance is based on a wealth of dose - response relationship data from four phase II studies of secukinumab in psoriasis (CAIN457A2102, CAIN457A2211,CAIN457A2212, CAIN457A2220), and the results from several phase III studies (CAIN457A2302, CAIN457A2303, CAIN457A2304,CAIN457A2307, CAIN457A2308, CAIN457A2309); ~4160 subjects randomized, and ~3310 subjects exposed to secukinumab).

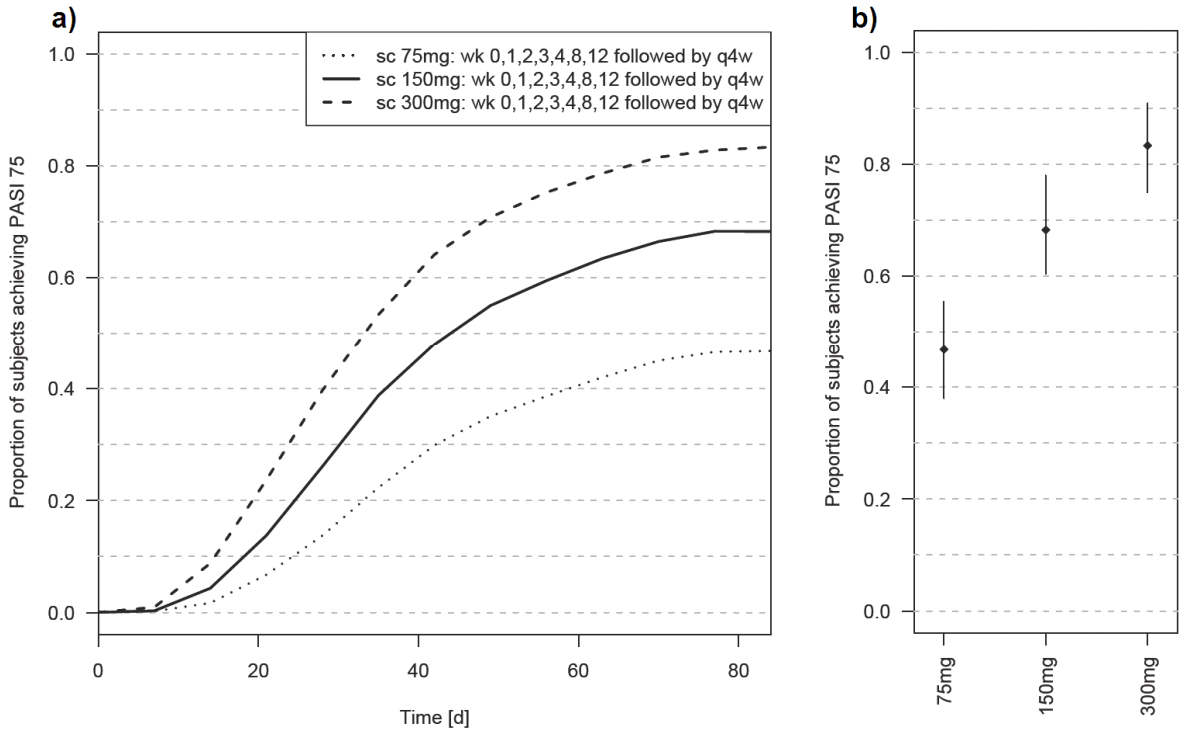
The proposal to use a dose of 300 mg s.c. administered with a weekly regimen (randomization, week 1, week 2, and week 3) followed by and treatment every 4 weeks thereafter (started at week 4) is based on the outcome of the Phase III studies (CAIN457A2302 and CAIN457A2303).

Study CAIN457A1101 in healthy Japanese male subjects did not show differential ethnic sensitivity to study materials. Hence, it is considered appropriate to treat the Asian population with the same doses as the non-Asian population.

The proposed induction regimen is also supported by analyses using data from four of the psoriasis studies (CAIN457A2102, CAIN457A2211, CAIN457A2212, and CAIN457A2220), which predict a notably better PASI 75 response rate of the proposed loading regimen after twelve weeks of treatment (see Figure 3-2) when compared to the response rates observed in study CAIN457A2211. In contrast, the predicted efficacy of a 75 mg dose also depicted in the graph does not promise to deliver acceptable efficacy.

[redacted]

Figure 3-2 Simulated PASI 75 response rates



a) Simulated PASI 75 response rates for the two doses proposed to be utilized in phase III (150 mg and 300 mg), plus for the rejected dose of 75 mg, for a treatment duration of twelve weeks with the proposed induction regimen (subcutaneous administration at Weeks 0, 1, 2, 3, 4, and 8).

b) Shown are the simulated response rates at the time point of twelve weeks, with the respective 95% prediction intervals.

The purpose of a maintenance regimen is to maintain subjects within clinically meaningful limits of responsiveness to the treatment. For psoriasis, successful maintenance is usually defined as maintaining the subjects on PASI 75 response at least.

Secukinumab 300 mg has been accepted as the recommended dose in all countries with a regulatory approval in psoriasis to date.

3.4 Rationale for choice of comparator

Due to the nature of psoriasis and the outcome measures used (PASI and IGA mod 2011 scores), a placebo arm is necessary to obtain reliable efficacy measurements. Moreover the inclusion of a placebo group is in accordance with health authority guidelines and feedback (see CHMP guidelines for psoriasis (CHMP/EWP/2454/02 2004). The choice of placebo control is a standard requirement to ascertain study sensitivity due to the seasonal and fluctuating character of chronic plaque-type psoriasis.

The continuation of the placebo group up to the primary endpoint at Week 12 is accepted for the indication of psoriasis. Subjects who do respond to placebo treatment (based on achievement of a PASI 75 response) will remain in the placebo arm beyond Week 12 and not

be re-assigned to secukinumab for the maintenance period, as they do not require active treatment. This will ensure continuous blinding of allocation beyond the induction period.

3.5 Purpose and timing of interim analyses/design adaptations

A Week 16 analysis is planned after all subjects have completed their Week 16 visit. This analysis will include primary endpoint data analysis at Week 12 visit, and in addition, Week 16 visit data [redacted]. There is no intention to modify study design based on the Week 16 analysis. Additional subsequent interim analyses may be conducted to fulfill any requests from Health Authorities. Full analysis of all data will be performed at the end of the study.

3.6 Risks and benefits

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

Non-clinical studies and phase 2 and 3 clinical studies in adults have not shown any impediment to using secukinumab subcutaneously in human. In total approximately 4,500 patients with moderate to severe plaque psoriasis were included in studies in the registration program. This included 3,430 patients treated with secukinumab in 10 phase 2/3 studies, 2,727 of whom were treated for at least 6 months and 2,029 of whom were treated for at least 48 weeks.

In adult studies, secukinumab has shown an excellent 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 and placebo with a rapid onset of action in the etanercept and placebo-controlled studies, CAIN457A2302 and CAIN457A2303.

Potential risks for subjects are as outlined in the approved product labeling. At this time, safety data including (1) AE data, laboratory parameters, available immunogenicity data from the completed studies, and (2) SAE data from the phase 3 studies do not show any other safety risk apart from the approved safety profile. The safety data from the completed and ongoing studies demonstrate a good safety profile which included an observed risk of infections in particular candida infections, neutropenia or hypersensitivity reactions that can be seen with administration of foreign proteins. Most of the infections were non-serious, mild to moderate in severity, clinically easily manageable and did not lead to treatment discontinuation. Cases of neutropenia were uncommon, generally mild to moderate and transient and did not lead to treatment discontinuation, and only a few cases were temporally associated with non-serious infections.

Subjects with pre-existing malignancies within the past 5 years are generally excluded from studies with secukinumab although there is no scientific basis to suggest that secukinumab would increase the risk for malignancies.

[redacted]

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

Subjects of Asian ethnicity who suffer from psoriasis have been included in several phase III studies. Across studies, subjects have been recruited in India, Japan, the Philippines, Singapore, South Korea, Taiwan, and Vietnam. Study CAIN457A1101 in healthy Japanese male subjects did not show differential ethnic sensitivity to study materials.

4 Population

The study population will consist of a representative group of male and female adult with moderate to severe chronic plaque-type psoriasis, poorly controlled by topical treatments and/or phototherapy and/or previous systemic therapy.

Disease severity in these subjects must justify systemic treatment. The requirement of PASI of at least 12 AND IGA mod 2011 of at least 3 AND a total BSA of minimum 10% reflects published guidelines (CHMP/EWP/2454/02 2004) and the outcome of discussions with health authorities. It is expected that between 10% and 30% of the recruited subjects will have psoriatic arthritis as comorbidity.

Approximately 536 subjects will be randomized in a 2:1:1 ratio into one of three treatment groups (secukinumab 300 mg, secukinumab 150 mg or placebo group) at approximately 45 study sites. As this study may be used to support the registration of secukinumab in China and other countries, the majority of the patients will be enrolled in China, for example: approximately 80% from China and the rest from other countries. Anticipating a screen failure rate around 30%, it is planned to screen a total of around 766 subjects. Subjects who drop out after randomization 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 communicate with the investigator and comply with the requirements of the study 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 and women 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 Baseline.
4. Moderate to severe psoriasis as defined at Baseline by:
   - PASI score of 12 or greater, **and**
   - IGA mod 2011 score of 3 or greater (based on a scale of 0 – 4), **and**
   - Body Surface Area (BSA) affected by plaque-type psoriasis of 10% or greater.
5. Candidate for systemic therapy. This is defined as a subject having moderate to severe chronic plaque-type psoriasis that is inadequately controlled by:
   - topical treatment, and/or

[redacted]

- 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 patients.

1. Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis) at Screening or Baseline.
2. Drug-induced psoriasis (i.e., new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium) at Baseline.
3. Ongoing use of prohibited treatments. Washout periods detailed in the protocol have to be adhered to (Table 5-1). Subjects not willing to limit UV light exposure (e.g., sunbathing and / or the use of tanning devices) during the course of the study will be considered not eligible for this study since UV light exposure is prohibited.

   Note: administration of live vaccines 6 weeks prior to Randomization or during the study period is also prohibited.
4. Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor.
5. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations
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 hCG laboratory test.
7. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective 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 a surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the 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 (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
   - Use of oral, injected or implanted hormonal methods of contraception or other forms or hormonal contraception that have complete efficacy (failure < 1%), e.g., hormone

[redacted]

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 12 weeks before taking study treatment.

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

- 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms), or
- Surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

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 renders the subject unsuitable for the trial or puts the subject at increased risk, including any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol
9. 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 status of class III or IV).
    - Subjects with a serum creatinine level exceeding 2.0 mg/dl (176.8 µmol/L).
    - Screening total white blood cell (WBC) count <2,500/µl, or platelets <100,000/µl or neutrophils <1,500/µl or hemoglobin <8.5 g/dl at screening
10. Chest X-ray, computed tomography (CT scan), or MRI with evidence of ongoing infectious or malignant process, obtained within 12 weeks prior to screening, and evaluated by a qualified physician.
11. Active systemic infections during the last two weeks (exception: common cold) prior to Baseline or any infection that reoccurs on a regular basis.
12. History of chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuantiFERON® TB-Gold test (QFT) at screening. Subjects with a positive or indeterminate QFT result may participate in the study if full tuberculosis work up (according to local practice/guidelines) was completed within 12 weeks prior to Baseline and establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local country guidelines prior to Baseline.
13. History or current infection with human immunodeficiency virus (HIV) or hepatitis C; or current hepatitis B infection

[redacted]

14. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for Bowen's disease, 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 six months before Baseline.
17. History of hypersensitivity to any of study drug constituent

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Novartis will supply the following study treatments:

- Investigational therapy: secukinumab
- Reference therapy: placebo

Secukinumab 150 mg syringes for s.c. injection will be provided in a 150mg 1 mL pre-filled syringe.

Secukinumab placebo for s.c. injection will be provided as a 1 mL pre-filled syringe matching the appearance of 150 mg secukinumab syringe; each placebo pre-filled syringe contains a mixture of inactive excipients, matching the composition of the secukinumab 150 mg dose.

5.1.2 Additional treatment

No additional treatment beyond investigational treatment described in Section 5.1.1 is used in this trial.

5.1.3 Treatment arms

At Baseline, approximately 536 subjects will be assigned to one of the following 3 treatment arms in a ratio of 2:1:1:

- **Secukinumab 300 mg regimen group**: secukinumab 300 mg (two injections of the 150 mg dose) administered at Baseline, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and Placebo (two injections per dose) administered at Weeks 13, 14, and 15.
- **Secukinumab 150 mg regimen group**: secukinumab 150 mg (one injection of the 150 mg dose + one injection of placebo) administered at Baseline, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and Placebo (two injections per dose) administered at Weeks 13, 14 and 15.
- **Placebo group**: placebo secukinumab (two injections per dose) administered at Baseline, Weeks 1, 2, 3, 4, and 8.

[redacted]

Based on their response to the treatment during the Induction epoch of the study, assessed at the Week 12 visit, subjects on placebo will either remain on placebo during the Maintenance epoch of the study or be re-assigned to secukinumab 300 mg, as follows:

- **Placebo PASI 75 Non-responder (**per definition in Section 6.4.2**):** secukinumab 300 mg (two injections of the 150 mg dose) administered at Weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
- **Placebo PASI 75 Responder (**per definition in Section 6.4.2**):** placebo secukinumab (two injections per dose) administered at Weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44 and 48.

5.2 Treatment assignment and randomization

At Baseline visit all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. Randomization will be stratified by geographical region and presence of psoriatic arthritis collected at the Randomization Visit. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient which will be used to link the subject to a treatment arm and will specify a unique medication number for the packages of investigational treatment to be dispensed to the subject. The randomization number will not be communicated to the caller.

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

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

5.3 Treatment blinding

Subjects, investigator staff, persons performing the assessments and data analyst will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study. (2) the identity of the treatments will be concealed by the use of investigational treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Unblinding will only occur in the case of subject emergencies (see Section 5.5.8) and at the conclusion of the study.

[redacted]

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

[redacted]

inadvertently for any reason. Study treatment must be discontinued after emergency unblinding. However for the purpose of Week 16 analysis as well as for any additional subsequent interim analyses that may be requested by Health Authorities, designated Novartis staff may be unblinded after Week 16 data base lock and subsequent locks, if any, to perform the analyses. Subjects, site staff, and study monitors will continue to remain blinded until study completion

5.4 Treating the patient

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

5.5 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 patient to register them into the IRT. The site must select the CRF book with a matching Subject Number from the OC/RDC system to enter data.

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

5.5.1 Dispensing the study drug

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

The study drug packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to one of the 3 treatment arms. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.2 Handling of study and additional treatment

5.5.2.1 Handling of study treatment

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

[redacted]

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

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.

5.5.2.2 Handling of additional treatment

Not applicable.

5.5.3 Instructions for prescribing and taking study treatment

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

- Two secukinumab 150 mg PFS (300 mg treatment arm) **OR**
- One secukinumab 150 mg PFS and one secukinumab placebo 150 mg PFS (150 mg treatment arm) **OR**
- Two secukinumab placebo 150 mg PFS (placebo treatment arm)

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

The syringes with the ready-to-use study treatment solution (PFS) will be provided. Study treatment will be administered subcutaneously throughout the study.

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

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

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

All doses of study treatment (secukinumab and placebo) will be administered at the study site, it is preferred that subject self-inject. However, if the subject is not able or not willing to self-administer, administration will be performed by study site staff. At the randomization/baseline visit the subjects will be instructed by the site staff walking them through the "Patient Instructions For Self-Administration" on how to self-inject via PFS. For subjects willing to self-inject, the first administration should be performed under guidance and supervision of a site staff member.

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.

[redacted]

At each site visit, all study assessments, including the completion of [redacted]
Patient's global assessment (PtGA) Disease Activity and PtGA Pain questionnaires (as reported by subjects), should be completed prior to the injection of study treatment.

All dates and times of injections during the study must be recorded on the Dosage Administration Record eCRF.

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

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

5.5.4 Permitted dose adjustments and interruptions of study treatment

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

5.5.5 Rescue medication

Rescue medication for psoriasis is not permitted in this study.

5.5.6 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies eCRF.

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

5.5.7 Prohibited medication

Use of any treatments displayed in Table 5-1 that could confound the efficacy are NOT allowed during the study for any indication and wash-out periods for these treatments are indicated in Table 5-1.

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

The use of the treatments listed in Table 5-1 is prohibited AFTER randomization for any indication, including psoriasis. These treatments need to be washed out before randomization as indicated. If the use of these treatments is required, then the subject should NOT be randomized into the study. If a prohibited treatment listed in Table 5-1 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, if the subject's use during the study of a prohibited treatment listed in Table 5-1 presents undue safety risk for the subject, the subject should be discontinued from study treatment as per Section 5.6.2. If the subject

[redacted]

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

During the screening, subjects will be allowed to use some active topical treatments for any indication in the following body regions: face, scalp, and genito-anal area. The active topical treatments are limited to: mild or moderate potency CS. The subject should stop using topical CS at least the day preceding randomization and is not allowed to use these topical CS for any indication at any time after randomization except as specified in the footnote for Table 5-1. Use of topical CS must be recorded on the Concomitant medications eCRF.

For all other body regions, a washout period of 2 weeks applies for all active topical treatments for any indication.

After the screening 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 5-1). The definition of "bland" excludes all topical medications that contain pharmacologically active ingredients. The use of bland emollients should be avoided during the 12 hours preceding a scheduled study visit.

Table 5-1 Prohibited treatment

Prohibited treatments[a, b]	Washout period (before Baseline)
Alefacept, briakinumab, efalizumab, ustekinumab	6 months
Biological immunomodulating agents other than the above (e.g., adalimumab, etanercept, infliximab)	12 weeks
Other systemic immunomodulating treatments[c] (e.g., MTX, cyclosporine A, corticosteroids, cyclophosphamide)	4 weeks
Other systemic psoriasis treatments (e.g., retinoids, fumarates, apremilast)	4 weeks
Photochemotherapy (e.g., PUVA)	4 weeks
Phototherapy (e.g., UVA, UVB)	2 weeks
Topical treatment which is likely to impact the signs and symptoms of psoriasis (e.g., corticosteroids[CS], vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids)[d,e, f]	2 weeks
Live vaccinations	6 weeks
Any investigational treatment (including IL23p19) or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)

[redacted]

Prohibited treatments[a, b]	Washout period (before Baseline)
Traditional Chinese medicine treatments of psoriasis and/or psoriatic arthritis[g]	4 weeks

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

[b] In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

[c] Including intra-articular or peri-articular injections. Note that inhaled CS with only a topical effect (e.g., to treat asthma) are not considered "systemic immunomodulating treatments" and are therefore acceptable as co-medication.

[d] Mild to moderate topical corticosteroids (CS) are allowed only during the screening , if used exclusively on the face, scalp and/or genito-anal area.

[e] Mild to moderate topical CS in the screening should be stopped at least the day prior to randomization.

[f] Topical corticosteroids and other topical treatments will be allowed during the maintenance epoch only if (all must apply):

- medication was started after the Week 12 visit was completed;
- medication was used for 14 consecutive calendar days or less;
- medication was used for an indication other than psoriasis and not on the area affected with psoriasis.

[g] Traditional Chinese medicine (TCM) is defined as a compendium of methods popular in Chinese tradition for the treatment of a wide range of conditions. TCM practitioners use herbal remedies, acupuncture, massage, mind-body and dietary therapies, and other methods. In the United States, TCM is considered part of complementary and alternative medicines (CAM).

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

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

Exposure to light

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

5.5.8 Emergency breaking of assigned treatment code

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

[redacted]

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

- protocol number
- patient number

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

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.

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 the patient has completed the last visit planned in the protocol.

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

5.6.2 Discontinuation of Study Treatment

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

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

If discontinuation occurs for any reason in the induction or maintenance epoch, the investigator/qualified site staff must make every effort to determine the primary reason for a subject's discontinuation from the study. This information will then be recorded by investigator/qualified site staff on the applicable end of study epoch eCRF.

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

- Emergence of the following AEs: AEs that in the judgment of the investigator/qualified site staff, taking into account the subject's overall status, prevent the subject from continuing study treatment (for example sepsis).
- Any laboratory abnormality that in the judgment of the investigator/qualified site staff, and taking into consideration the subject's overall status, prevents the subject from continuing study treatment.
- Pregnancy (see Section 6.5.6 and Section 7.4)
- Use of ongoing prohibited treatment as per recommendations in Section 5.5.8.
- Emergency unblinding.
- Any protocol deviation that results in a significant risk to patient's safety.

Subjects discontinued from study treatment will NOT be considered discontinued from the study. On the applicable end of treatment epoch eCRF (EOI and EOM completion eCRFs), the investigator/qualified site staff must record the date and primary reason for stopping study treatment.

[redacted]

At the time of the study treatment discontinuation visit, if it has been approximately 4 weeks post last dose of study treatment then the assessments described at the EOI Visit Week 12 (for early discontinuation during induction epoch) or the EOM Visit Week 52 (for early discontinuation during maintenance epoch) should be completed at this visit and the subject should then return per appropriate schedule for the visits F4 and F8.

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 EOI or EOM visit as appropriate, respectively, and then the subject should return per appropriate schedule for follow up visits F4 and F8.

The investigator must contact the IRT as soon as possible, to register the subject's early completion of the study (induction or maintenance epochs, respectively) due to study treatment discontinuation.

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.

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 patient's decision to withdraw his/her consent and record this information.

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

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

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

5.6.4 Loss to follow-up

For 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

[redacted]

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

5.6.5 Early study termination by the sponsor

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

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.

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

If the date of a TB work up is less than 12 weeks from the projected randomization date, then it is not required that the TB work up be repeated. However, the subject must repeat the Quantiferon® test performed by the central laboratory.

During the treatment period, subjects may be seen at an unscheduled visit, e.g., if they experience deterioration of psoriasis and/or psoriatic arthritis, or AEs that in the opinion of the investigator need intervention or repeated laboratory testing. During these unscheduled visits, study treatment will **NOT** be administered.

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

Subjects who discontinue study treatment before completing the study, and those who prematurely withdraw from the study for any reason should be scheduled for a study visit 4 weeks after their last study treatment administration, at which time all the assessments listed

[redacted]

for EOI (Week 12)/ EOM (Week 52) will be performed. Then, subjects should return to the study site for further assessments as indicated under the follow-up visits (F4 and F8).

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

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

Suggested order of assessments:

The recommended order of assessments, as applicable at the respective visits, is:

- Patient-reported outcomes (PROs) prior to any assessments made by the investigator, in the following order: [redacted] and in subjects with psoriatic arthritis only: [redacted] PtGA Disease Activity, PtGA Pain.
- Investigator assessments in the following order: IGA mod 2011, PASI, PhGA PsA Activity (in subjects with psoriatic arthritis only).
- Tender and swollen joint count*
- All remaining procedures (e.g., laboratory sample collection, vital signs) must be completed prior to study treatment administration.
- PASI and IGA mod 2011 assessments are recommended to be recorded in the eCRF before contacting IRT (at Baseline and Week 12 visit).
- Contact IRT to register the subject visit.
- Study treatment administration.

* At baseline tender and swollen joint count assessment will be completed before initiating PROs and PhGA PsA in order to decide if a subject should complete the PROs related to psoriatic arthritis.

[redacted]

Table 6-1 Assessment schedule

Epoch	Scr	Induction							Maintenance													Unscheduled visit[d]	FU[c]	
Week (relative to baseline)	**≥-4 to ≤-1**	B	1	2	3	4	8	12[a]	13	14	15	16	20	24	28	32	36	40	44	48	52[b]		56	60
Day	**≥-28 to ≤-7**	1	8	15	22	29	57	85	92	99	106	113	141	169	197	225	253	281	309	337	365		393	421
Informed consent	X																							
Subject demographics	X																							
Inclusion / exclusion criteria[1]	X	S																						
Smoking history	X																							
Medical history of Ps and PsA / previous therapies	X																							
Other medical history, including Cardiovascular history, and prior medications	X																							
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	S	S				S	S	S				S	S	S			S				S	S	S	S
Height	X																							
Weight	X	X						X						X			X				X	X		X
Vital signs	X	X				X	X	X				X	X	X			X				X	X	X	X
Urinalysis (local laboratory)	X	X						X						X							X			
Hematology / blood chemistry[2]	X	X		X		X	X	X		X		X	X	X			X			X	X	X	X	X
Fasting lab samples[2]: plasma glucose, lipid panel		X																						
hsCRP[2]		X						X						X			X				X	X		X

[redacted]

Epoch	Scr	Induction							Maintenance												Unscheduled visit[d]	FU[c]	
Week (relative to baseline)	**≥-4 to ≤-1**	B	1	2	3	4	8	12[a]	13	14	15	16	20	24	28	32	36	40	44	48	52[b]		56	60
Day	**≥-28 to ≤-7**	1	8	15	22	29	57	85	92	99	106	113	141	169	197	225	253	281	309	337	365		393	421
[redacted]																								
QuantiFERON® TB-Gold test[2]	X[3]																					X		
Hepatitis and HIV screen[9]	X																							
Serum pregnancy test[2,4]	X																					X[4]		
Urine pregnancy test (local lab)[4]		X						X						X			X				X	X		X
Chest X-ray[6]	S																							
ECG (standard 12 lead)	X							X						X			X				X	X		X
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IGA mod 2011	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																								
CASPAR[10]		X																						
Swollen/tender joint count[8, 10]		X				X		X						X							X			
PtGA-A (VAS)[8]		X				X		X						X							X			
PtGA-P (VAS)[8]		X				X		X						X							X			
PhGA PsA (VAS)[8]		X				X		X						X							X			
ESR[8,11]		X				X		X						X							X			
HAQ-DI[8]		X				X		X				X		X			X				X	X		
Adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Epoch	Scr	Induction							Maintenance													Unscheduled visit[d]	FU[c]	
Week (relative to baseline)	**≥-4 to ≤-1**	B	1	2	3	4	8	12[a]	13	14	15	16	20	24	28	32	36	40	44	48	52[b]		56	60
Day	**≥-28 to ≤-7**	1	8	15	22	29	57	85	92	99	106	113	141	169	197	225	253	281	309	337	365		393	421
SAE assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization via IRT[12]		X						X																
Dispense study treatment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Screening epoche-CRF Completion		X																						
End of induction: submit induction epoch completion eCRF and call IRT								X[a]																
End of maintenance: submit maintenance epoch completion eCRF and call IRT																					X			
End of follow-up: submit follow-up epoch completion eCRF																								X

B=Baseline, Scr=screening, hsCRP=high sensitivity C-reactive protein, eCRF=electronic case report form, SAE=serious adverse event, [redacted] VAS=visual analog scale, IRT=interactive response technology, Ps=psoriasis, PsA=psoriatic arthritis

X = to be recorded in the clinical database; S = to be recorded in source documentation only

[a] All induction epoch assessments must be performed prior to dosing.

[b] During Visit Week 52, subjects will have their last assessments performed for the maintenance treatment epoch and will enter the post-treatment follow up epoch or join a possible extension study, if available (only applicable for completers of the maintenance epoch. Visit Week 52 is also to be done for early study discontinuations from the maintenance epoch.

[c] All subjects who discontinue prematurely from the induction or maintenance epochs should enter the follow-up epoch.

[redacted]

Epoch	Scr	Induction							Maintenance												Unscheduled visit[d]	FU[c]	
Week (relative to baseline)	**≥-4 to ≤-1**	B	1	2	3	4	8	12[a]	13	14	15	16	20	24	28	32	36	40	44	48	52[b]		56	60
Day	**≥-28 to ≤-7**	1	8	15	22	29	57	85	92	99	106	113	141	169	197	225	253	281	309	337	365		393	421

[d] The assessment(s) to perform at unscheduled visits are at the investigator's discretion.

[1] The outcome of these assessments is filed with the source documentation. Data regarding the Inclusion/Exclusion screen are captured in the eCRF.

[2] Samples will be shipped to and analyzed by a central laboratory.

[3] If the first QuantiFERON® TB-Gold In-Tube test is indeterminate, the investigator may choose to perform a second QuantiFERON® TB-Gold In-Tube test (as part of an unscheduled visit) or refer the subject for tuberculosis workup per local guidelines. If the result of any QuantiFERON® TB-Gold In-Tube test is "positive" or the results of 2 successive QuantiFERON® TB-Gold In-Tube tests 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). 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. No QuantiFERON® TB-Gold In-Tube test is to be conducted after the subject is randomized.

[4] In case of positive urine pregnancy test, study treatment must be withheld and serum pregnancy test is performed at the same visit. Urine testing for pregnancy is not required for sterile or post-menopausal women.

[5] [redacted]

[6] No new chest X-ray is needed in subjects with chest X-ray or chest CT scan or MRI performed within 12 weeks of screening.

[7] [redacted]

[8] ACR criteria component. Only in subjects with psoriatic arthritis (PsA) and who have at least 3 tender and 3 swollen joints at baseline (at baseline tender and swollen joint assessment will be performed for all subjects with medical history of PsA).

[9] Screening for hepatitis and HIV is required. Hepatitis testing will include hepatitis B surface antigen (HBsAg) and HCV antibodies. Positive HIV screening will be confirmed by alternative technique available at the laboratory, e.g., Western blot.

[10] Conducted at baseline on all subjects with medical history of PsA.

[11] Central lab will supply kits for ESR however the ESR test will be conducted at the site.

[12] The PASI score and Investigator's Global Assessment eCRF must be completed prior to contacting IRT for randomization. At the screening visit, the investigator must confirm that the subject meets IGA mod 2011, PASI and BSA eligibility before randomizing the subject. At the Week 12 visit, PASI 75 status from the PASI score eCRF must be available for entry into IRT.

[redacted]

6.1 Information to be collected on screening failures

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

If a subject discontinues before entering the double-blind treatment period, the IRT must be notified within 5 days and the reason for not being randomized will be entered on the Screening Phase Disposition electronic Case Report Form (eCRF). The Screening visit date, the Demography eCRF, Informed Consent eCRF, Inclusion/Exclusion Criteria eCRF and Subject rescreening eCRF must be completed. The Adverse Event eCRF and an SAE form should be completed for any serious adverse event (SAEs) that occurred during the screening epoch. The Withdrawal of consent eCRF should be completed if consent was withdrawn during the screening epoch before the subject was randomized. The Death eCRF should be completed in the case of a death during the screening epoch.

All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

6.2.1 Demographics

Subject demographic data will include: date of birth (might be restricted to the year only due to applicable local data protection regulations), sex, race, ethnicity, and child-bearing potential (for females only).

6.2.2 Psoriasis medical history / Previous psoriasis therapies

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

- The start date of plaque psoriasis.
- The date of first diagnosis of psoriatic arthritis (by a physician).
- The previous treatments of psoriasis/psoriatic arthritis (including previous use of biologic therapies, as well as phototherapy and/or photo chemotherapy) and the reason for discontinuation.
- Relevant psoriasis/psoriatic arthritis medical history and current medical condition, e.g., status of TNFα inhibitor responsiveness.

6.2.3 Smoking history

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

6.2.4 Co-morbidities – cardiovascular medical history

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

[redacted]

6.2.5 Relevant medical history/current medical conditions

Relevant medical history and current medical conditions present before signing the informed consent should be recorded in the Medical History eCRF.

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

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

Chest X-ray

No new chest X-ray is needed in subjects with chest X-ray or chest CT scan or MRI performed within 12 weeks of screening. This is aimed to detect ongoing infection and particularly tuberculosis or malignancy.

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

Hepatitis and human immunodeficiency virus (HIV) screen

Screening for hepatitis and HIV is required.

6.2.6 Determination of the tuberculosis status

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

QuantiFERON TB-Gold In-Tube assay

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

Positive or indeterminate tests must be recorded on the source document. The workflow of sample handling in case of positive or indeterminate test results is provided in Figure 6-1.

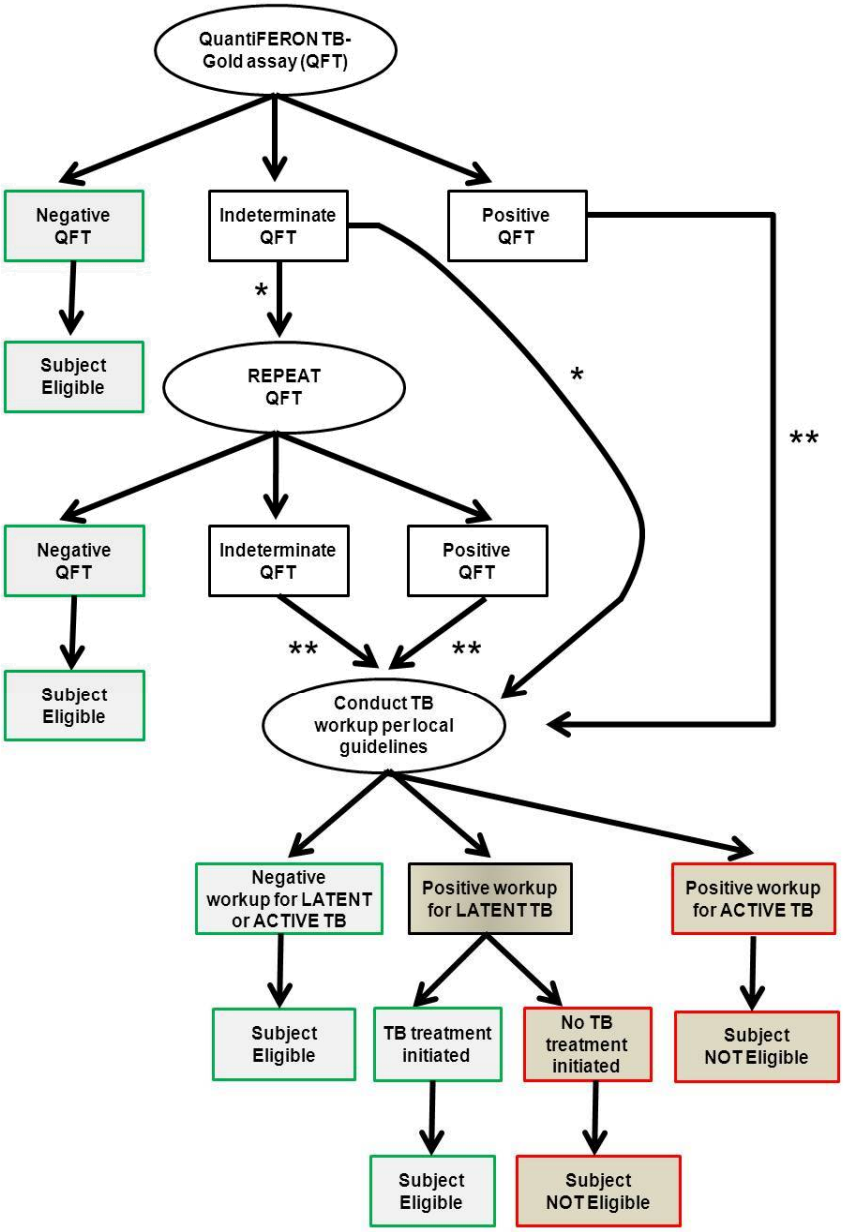
- If the test result is **negative**, the subject may be randomized.
- If the test result is **positive**, the investigator should perform workup for the test result as per local procedures. If a TB workup was conducted prior to screening the subject, results of the workup can be used to assess eligibility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

[redacted]

  - Subjects positive for active TB per workup are not eligible for the study.
  - Subjects negative for TB (no signs of latent or active TB) per workup may be randomized to the trial.
- If the test result is **indeterminate**, the investigator **may repeat the test once or may proceed directly to perform workup** for the test result as per local procedures. This action is at the discretion of the investigator. If a TB workup was conducted prior to the screening the subject, results of the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to randomization.
  - If the second test is negative, the subject may be randomized.
  - If the second test is positive or indeterminate, the investigator should perform workup as 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. Subjects **positive** for **active** TB per workup **are not eligible** for the study. Subjects negative for TB per workup (no signs of latent or active TB) may be randomized to the trial.
- If eligibility is being assessed with only 1 test result and a TB workup (i.e., no second TB test will be performed), the TB test to assess eligibility must have been done via the central laboratory for the study within the screening epoch (within 4 weeks prior to randomization) and TB workup will only be considered if it was completed **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 per workup (no signs of latent or active TB) may be randomized to the trial.

[redacted]

Figure 6-1 Tuberculosis screening flowchart



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

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

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

6.2.7 Diagnosis of psoriatic arthritis (PsA) – CASPAR

All subjects with a medical history of PsA during the screening epoch will be assessed to establish if there is a diagnosis of PsA per the ClASsification of Psoriatic ARthritis (CASPAR) criteria according to (Taylor et al 2006). The CASPAR assessment data are to be available to the study investigator prior to the randomization visit as specified in Table 6-1.

[redacted]

In order to establish the diagnosis of psoriatic arthritis, at least 3 points out of the five ClASsification of Psoriatic ARthritis (CASPAR) criteria according to (Taylor et al 2006) must be met (see Appendix 2):

1. Evidence of current psoriasis, or personal history of psoriasis, or a family history of psoriasis
   - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist **(2 points)**
   - Personal history of psoriasis is defined as a history of psoriasis that may be obtained from a subject, family physician, dermatologist, rheumatologist, or other qualified health care provider (**1 point**, unless current psoriasis was present)
   - A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to the subject (**1 point**, unless current psoriasis was present or personal history of psoriasis
2. Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination (**1 point**)
3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by an Enzyme-Linked Immunosorbent Assay (ELISA) or nephelometry, according to the local laboratory reference range (**1 point**)
4. Either current dactylitis (defined as swelling of an entire digit), OR a history of dactylitis (recorded by a rheumatologist) **(1 point)**
5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot **(1 point).**

6.2.8 Other baseline characteristics

Baseline characteristic data to be collected on all subjects include (all laboratory results are central except where indicated): ECG, vital signs; hematology; clinical chemistry; local urinalysis; serum pregnancy test; past medical history record of HIV, hepatitis B or hepatitis C status; [redacted] PASI; IGA mod 2011; [redacted]; Swollen/tender joint count, HAQ-DI, PtGA-Activity, PtGA-Pain and PhGA PsA.

6.3 Treatment exposure and compliance

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

6.4 Efficacy

All efficacy assessments should be performed by qualified site personnel. The following order should be applied when performing the efficacy assessments at study visits:

- Investigator's Global Assessment for general psoriasis (IGA mod 2011; scale from 0 – 4)

[redacted]

- Psoriasis Area and Severity Index (PASI; score from 0 – 72)
- ACR response (in subjects with PsA)

6.4.1 Investigator Global Assessment (IGA mod 2011)

IGA mod 2011 will be conducted for overall psoriatic disease as indicated in Table 6-1 and Table 6-2. It is recommended that the same evaluator conduct the assessment throughout the study whenever possible.

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

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

The IGA mod 2011 score will be recorded in the 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.

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

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

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

The PASI assessment will be completed as indicated in Table 6-1. Whenever possible, the same evaluator should perform this PASI assessment at all visits.

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for PASI assessment). The following calculations will be done: Each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper

[redacted]

limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added up to estimate the total BSA affected by plaque-type psoriasis. The PASI scoring system is further described in Table 6-3.

A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) will be derived as indicated in Table 6-3. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

1. The neck is assessed as part of the head.
2. The axillae and groin are assessed as part of the trunk.
3. The buttocks are assessed as part of the lower limbs.

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

Table 6-3 The PASI scoring system

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

[redacted]

	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.

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

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

The keys for the letters are provided in Table 6-3.

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

A subject will be considered as a PASI 75 responder if he/she achieves a reduction of 75% or more of the PASI score, compared to baseline, at a given time point.

At the end of the induction epoch, the PASI score will be calculated and subjects will be classified as PASI 75 responders or PASI 75 non-responders according to the definitions stated below. Therefore, at EOI Visit Week 12, the investigator or qualified designee should ensure that all the information required for the PASI calculation was entered into the PASI Score eCRF at EOI Visit Week 12 and that a PASI score and PASI 75 responder status is available prior to contacting IRT. The investigator or qualified designee will enter the EOI Visit Week 12 PASI 75 responder status into the IRT system at EOI Visit Week 12 prior to dosing.

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

- **PASI 50 response:** subjects achieving ≥ 50% improvement (reduction) in PASI score compared to baseline
- **PASI 75 response:** subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline
- **PASI 90 response:** subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline
- **PASI 100 response/remission:** complete clearing of psoriasis (PASI=0)

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

[redacted]

[redacted]

[redacted]

6.4.5 Assessment of the American College of Rheumatology (ACR) response in subjects with psoriatic arthritis

Assessments related to psoriatic arthritis will be performed as indicated in Table 6-1. Evaluations to determine ACR response (ACR 20/50/70) include tender and swollen joint counts, HAQ-DI, PtGA Activity, PtGA Pain, PhGA PsA and acute phase reactant (ESR and hsCRP).

The elements of the ACR scoring system are used in the same way as in standard trials of rheumatoid arthritis, with the exception of the number of joints tested, to include distal interphalangeal joints of the feet and carpometacarpal joints of the hands, i.e., 76 joints for tenderness and 78 joints for swelling. ACR 20, 50 or 70 responses correspond, respectively, to at least 20%, 50% or 70% improvement in comparison with baseline in the number of tender and swollen joint counts, in addition to similar improvements in at least three of five domains-HAQ-DI measure of disability, acute phase reactant (CRP or ESR) and the VAS scores of PtGA Activity, PtGA Pain and PhGA PsA.

6.4.6 Appropriateness of efficacy assessments

The PASI score, the assessment of the severity of the psoriasis symptoms and the extent to which the subject's body area is affected by the disease, is considered acceptable by health authorities (CHMP/EWP/2454/02 2004) to assess efficacy in conjunction with Investigator's Global Assessment mod 2011 (IGA mod 2011). The efficacy assessments in patients with PsA co-morbidity are standardized measures used across many psoriatic arthritis trials and may be used to complement the knowledge base pertaining to the condition, as well as for regulatory filing.

6.5 Safety

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

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

[redacted]

- Pregnancy

[redacted]

6.5.1 Physical examination

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

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

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

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

6.5.2 Vital signs

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

After the subject has been sitting for about five minutes, with back supported and both feet placed on the floor, systolic and diastolic **blood pressure will be measured twice** and will be recorded in the source documentation (measurements separated by 1 to 2 minutes) using a validated device, with an appropriately sized cuff (Mancia et al 2007). In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. 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 < 120mmHg, and a diastolic blood pressure of 60 to <80 mmHg under measurement conditions as outlined above. Notable blood pressure will be hypertension (systolic ≥ 140 mmHg and/or diastolic >90 mmHg) or hypotension (systolic <90 mmHg and/or diastolic <60 mmHg). A blood pressure indicative of pre-hypertension (systolic 120 to <140 mmHg and/or diastolic 80 to < 90 mmHg) will not be regarded as notable (Chobanian et al 2003).

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

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

6.5.3 Height and weight

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

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

[redacted]

6.5.4 Laboratory evaluations

Subjects should avoid smoking within the hour preceding blood drawing.

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

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

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

6.5.4.1 Hematology

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

6.5.4.2 Clinical chemistry

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

6.5.4.3 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 appropriate eCRF page for each subject. Standard dipstick measurements for specific gravity, protein, glucose, pH, blood, urine blood dipstick (non-hemolyzed), urine blood dipstick (hemolyzed), bilirubin, ketones and WBC will be done at baseline as indicated in Table 6-1.

6.5.5 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed as indicated in Table 6-1.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents.

Although there is no exclusion criterion based on ECG results, the baseline ECG at the Randomization Visit must be reviewed locally for major abnormalities prior to dosing.

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

6.5.6 Pregnancy

A serum β-hCG test will be performed in all women of child bearing potential as indicated in Table 6-1.

All women who are not sterile and all women who are not post-menopausal at screening will have a local urine pregnancy test as indicated in Table 6-1.

Any woman with a confirmed positive pregnancy test during screening is not eligible for randomization. A positive urine pregnancy test during the treatment periods of the study

requires immediate interruption of study treatment until a serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, the subject must be discontinued from the study treatment.

6.5.7 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic immunomodulating agent in psoriasis.

6.6 Other assessments

The following additional assessments will be performed:

- Clinician Reported Outcomes (swollen/tender joint count; PhGA PsA)
- Patient Reported Outcomes ([redacted] the following only in subjects with PsA- HAQ-DI, Patient's global assessment of disease activity (Pt-GA Activity) and Patient's global assessment of pain (Pt-GA Pain)
- Fasting laboratory evaluations
- [redacted]

6.6.1 Clinical Outcome Assessments (COAs)

6.6.1.1 Clinician Reported Outcomes (ClinRO)

Tender 78-joint count and swollen 76-joint count (subjects with PsA only)

The assessment of tender (78 joints) and swollen (76 joints) joint count will be performed as indicated in Table 6-1 at baseline for all subjects with a medical history of PsA and later only for subject with PsA and who have at least 3 tender and 3 swollen joints at baseline. Whenever possible, the same evaluator should perform this assessment at all required visits.

The distal interphalangeal joints of the feet and the two first carpometacarpal joints of the hands are added to the usual ACR joint count of 68 tender and 66 swollen joints, to yield 78 and 76 joint counts, respectively. Thus, the joints assessed for tenderness include the 8 distal interphalangeal, 10 proximal interphalangeal 10 metacarpophalangeal, and the 2 first carpometacarpal joints of the hands, and 10 metatarsophalangeal, 10 proximal interphalangeal and 8 distal interphalangeal joints of the feet, the 2 wrists, 2 elbows, 2 shoulders, 2 acromioclavicular, 2 sternoclavicular, 2 temporomandibular, 2 hip, 2 knee, 2 talo-tibial, and 2 mid-tarsal joints. All of these except for the hips are assessed for swelling. Joint tenderness and swelling to be graded present (1) or absent (0). Synovial fluid and/or soft tissue swelling but not bony overgrowth represents a positive result for swollen joint count. Dactylitis of a digit in the foot or hand counts as one tender and swollen joint.

Data are recorded for the joints which are positive. Data are recorded for tender and swollen joints (right or left side), i.e. a box (no, yes or not applicable) needs to be ticked for all joints. In addition, also the total number of tender and swollen joints (right and left) and the total number of right and left missing or not applicable tender and swollen joints will be recorded on the Tender and Swollen Joint Count (78/76) eCRF.

[redacted]

Physician's global assessment of disease activity, PhGA PsA (subjects with PsA only)

When a subject has PsA at baseline defined as at least 3 points out of the CASPAR criteria and at least 3 tender and 3 swollen joints at baseline, the rheumatologist or a qualified trained physician will complete the Physician's Global Assessment of disease activity (PhGA PsA) using a visual analog scale (VAS) as indicated in Table 6-1. Whenever possible, the same evaluator should perform this assessment at all indicated visits.

The investigator will be presented with the question '*Considering all the ways psoriatic arthritis affects your patient, please indicate by tapping on the horizontal line how would you rate his or her current condition?'* The investigator or qualified designee will then record the response using 100 mm VAS ranging from "very good" to "very poor" on the VAS.

To enhance objectivity, the investigator or qualified designee must not be aware of the specific subject assessments [redacted] HAQ-DI, PtGA Activity and the PtGA Pain, prior to performing his own assessment on that subject.

6.6.1.2 Patient Reported Outcomes (PRO)

The impact of study treatment on patient's health status will be assessed by the following measures:

[redacted]

Health Assessment Questionnaire- Disability Index (HAQ-DI) (subjects with PsA only)

The Health Assessment Questionnaire (HAQ©) was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a subject's level of functional ability and activity restriction. Although originally developed for use in subjects with rheumatic disease, the HAQ has been employed across a large variety

[redacted]

of disease areas. The disability assessment component of the HAQ (Health Assessment Questionnaire© – Disability Index), the HAQ-DI, assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 items in eight categories of functioning including dressing & grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to …" perform a particular task. Each item is scored on a 4-point scale from 0 to 3, representing normal (without any difficulty [0]), with some difficulty (1), with much difficulty (2), and unable to do (3). The HAQ-DI also includes questions about the use of 'aids or devices' and aid from other people to supplement the answers given to the 20 items.

The purpose of the HAQ-DI in this study is to assess the functional ability of subjects with PsA.

The HAQ-DI questionnaire will be completed as indicated in Table 6-1 by all subjects with PsA at baseline defined as at least 3 points out of 5 CASPAR criteria and at least 3 tender and 3 swollen joints at baseline.

Patient's global assessments (subjects with PsA only)

When a subject has PsA at baseline defined as at least 3 points of the CASPAR criteria and at least 3 tender and 3 swollen joints at baseline, the subject will be asked to complete the following non-validated instruments as indicated in Table 6-1:

- Patient's Global Assessment of disease activity (PtGA Activity)

  As indicated in Table 6-1, subject with PsA will be asked to complete the Patient's Global Assessment of disease activity (PtGA Activity) using a visual analog scale (VAS).

  The subject will be presented with the question '*Considering all the ways your psoriatic arthritis affects you, please indicate by tapping on the horizontal line how well you are doing today.'* The subject will then record a self-assessment of disease activity using 100 mm VAS ranging from "very good" to "very poor" on the VAS.
- Patient's Global Assessment of psoriatic arthritis pain (PtGA Pain)

  As indicated in Table 6-1, subject with PsA will be asked to complete the Patient's Global Assessment of psoriatic arthritis pain (PtGA Pain) using a visual analog scale (VAS).

  The subject will be presented with the question 'Please indicate by tapping on the horizontal line the most pain you had from your psoriatic arthritis over the last 24 hours'. The subject will then record pain associated with psoriasis using 100 mm VAS ranging from "no pain" to "unbearable pain" on the VAS.

Completed questionnaires will be reviewed and examined by the investigator only after the clinical efficacy assessments (PASI and IGA), for responses that may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaire but also for any unsolicited comments written by the subject. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7 of the protocol. Investigator should not encourage the subject to change the responses reported in the completed questionnaires.

6.6.1.3 Performance Outcomes (PerfO)

Not applicable.

[redacted]

6.6.1.4 Observer Reported Outcomes (ObsRO)

Not applicable.

6.6.1.5 Proxy Reported Outcomes

Not applicable.

6.6.2 Resource utilization

Not applicable.

6.6.3 Fasting Laboratory evaluations

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

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

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

6.6.3.1 Plasma glucose

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

6.6.3.2 Lipid panel

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

[redacted]

[redacted]

6.6.5 DNA sampling

Pharmacogenetics

Not applicable.

6.6.6 Other biomarkers

Not applicable.

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 patient at each visit during the study. Adverse events also may be detected when they are volunteered

by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- 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 patient 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 (yes/no)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met
- action taken regarding study treatment

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

- no action taken (e.g. further observation only)
- study treatment dosage increased/reduced
- study treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

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

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

[redacted]

include cases when a) a new type of psoriasis is diagnosed e.g. guttate psoriasis) or b) the worsening of psoriasis is so severe that a qualitatively different status is reached.

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

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

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

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (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

[redacted]

immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (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 patient safety, every SAE, regardless of causality, occurring after the patient 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 the 12 weeks period following the last administration of study treatment should only be reported to Novartis if the investigator suspects a causal relationship to study treatment. Any SAEs reported up to the subject's last visit will be reported in the AE eCRF. SAEs beyond that date will only be recorded in the Novartis Drug Safety and Epidemiology database.

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

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

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

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

[redacted]

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

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

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on 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 patient records, the accuracy of entries on the (e) CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study

treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the 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 patients/subjects will be disclosed.

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 database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff [or CRO working on behalf of Novartis] review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

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

[redacted]

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

ECG readings will be processed locally.

Randomization codes and data about all study drug(s) dispensed to the patient 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 database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

Data Monitoring Committee (DMC) is planned in this study. Details regarding the DMC will be available in the relevant DMC charter.

8.5 Adjudication Committee

An independent adjudication committee may be established. Details regarding the adjudication process will be available in the relevant Adjudication Committee charter.

9 Data analysis

The final analysis will be conducted on all subject data at the time the trial ends.

A Week 16 analysis is planned to be performed after all subjects have completed Week 16 visit. [redacted] Additional subsequent interim analyses may be performed to fulfill any requests from Health Authority.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Treatment groups for analyses will include:

- Induction epoch: secukinumab 150 mg, secukinumab 300 mg and placebo.
- Maintenance epoch: secukinumab 150 mg, secukinumab 300 mg and placebo, as well as placebo-secukinumab 300 mg.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

If not otherwise specified, p-values will be presented as two-sided p-values and two-sided confidence intervals will be displayed.

9.1 Analysis sets

The following analysis sets will be used in this trial:

[redacted]

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

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

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

9.2 Patient demographics and other baseline characteristics

Demographics and baseline characteristics

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

Medical history

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

9.3 Treatments

Study treatments

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

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

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

Prior and concomitant treatments

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

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

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

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

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

9.4 Analysis of the primary variable(s)

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

9.4.1 Variable(s)

The co-primary efficacy variables are PASI 75 response at Week 12 and IGA mod 2011 0 or 1 response at Week 12. The secondary variable is PASI 90 response at Week 12.

The analysis of the co-primary and secondary variables will be based on the FAS.

9.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypotheses for PASI 75 response at Week 12 and IGA mod 2011 0 or 1 response at Week 12 being tested is that any of the secukinumab groups are not superior to placebo in the proportion of subjects with PASI 75 response and IGA mod 2011 0 or 1 response at Week 12.

Let p_j denote the proportion of PASI 75 responders at Week 12 for treatment group *j* and r_j denote the proportion of IGA mod 2011 0 or 1 responders at Week 12 for treatment group *j*, *j*=0, 1, 2, where

- 0 corresponds to placebo,
- 1 corresponds to secukinumab 150 mg,
- 2 corresponds to secukinumab 300 mg.

The following hypotheses will be tested

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

H_2: $p_2 - p_0 \leq 0$ versus H_{A2}: $p_2 - p_0 > 0$,

H_3: $r_1 - r_0 \leq 0$ versus H_{A3}: $r_1 - r_0 > 0$,

H_4: $r_2 - r_0 \leq 0$ versus H_{A4}: $r_2 - r_0 > 0$.

In other words:

H_1: secukinumab 150 mg is not superior to placebo with respect to PASI 75 response at Week 12

H_2: secukinumab 300 mg is not superior to placebo with respect to PASI 75 response at Week 12

H_3: secukinumab 150 mg is not superior to placebo with respect to IGA mod 2011 0 or 1 response at Week 12

H_4: secukinumab 300 mg is not superior to placebo with respect to IGA mod 2011 0 or 1 response at Week 12

The primary endpoint (PASI 75 and IGA mod 2011 0 or 1 response at Week 12) will be evaluated using an exact logistic regression model with treatment group, baseline body weight, geographical region, presence of psoriatic arthritis, and baseline PASI score as explanatory

[redacted]

variables. Odds ratios will be computed for comparisons of secukinumab dose regimens versus placebo utilizing the exact logistic regression model fitted. In case of rates of 0% or 100% in one of the treatment groups, Fisher's exact test will be applied.

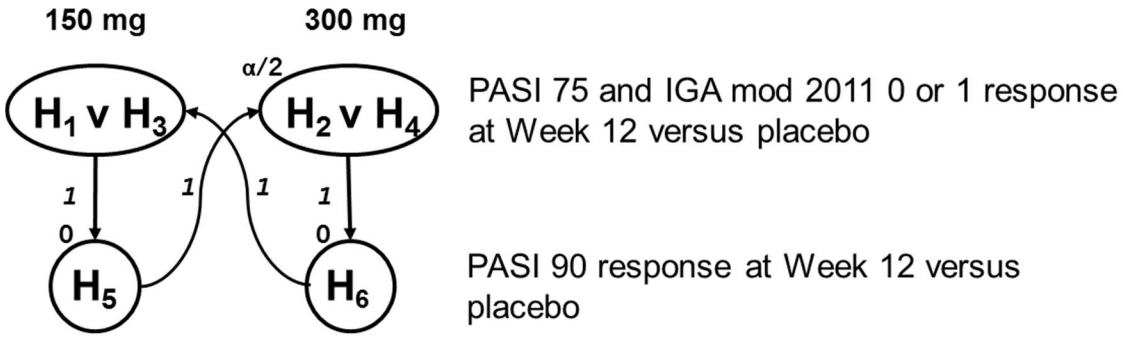
PASI 90 response at Week 12 will be evaluated analogously to PASI 75 and IGA mod 2011 0 or 1 response at Week 12 (i.e., exact logistic regression analysis) and the following hypotheses will be tested:

H_5: secukinumab 150 mg is not superior to placebo with respect PASI 90 response at Week 12

H_6: secukinumab 300 mg is not superior to placebo with respect PASI 90 response at Week 12

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

Figure 9-1 Testing strategy



One-sided p-values will be derived. The family-wise error will be set to α=2.5% (one-sided). The hypotheses are mapped into two sets (H1, H3, and H5) or (H2, H4, and H6) such that hypotheses within a set correspond to the same secukinumab dose regimen (150 mg or 300 mg). In essence, the type-I-error probability will be equally split for both sets of hypotheses and within each set the hypotheses are tested sequentially as follows:

Within each pair of hypotheses (H1 or H3) and (H2 or H4) each hypothesis is tested at α/2. Only if both hypotheses of a pair are rejected, the testing sequence will continue and the PASI 90 comparisons of secukinumab versus placebo are tested, H5 or H6 will be tested at α/2 (one-sided).

If all hypotheses within a set referring to a secukinumab dose regimen have been rejected, i.e., (H1, H3, and H5) or (H2, H4, and H6), the corresponding type-I-error probability can be passed on to the other group of hypotheses, and if needed, hypotheses can be retested at a new significance level.

9.4.3 Handling of missing values/censoring/discontinuations

Response variables based on PASI score and IGA mod 2011 score will be imputed with multiple imputation (MI) as primary imputation method for the missing values.

Multiple imputation (MI) is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Within this analysis the PASI score or IGA

[redacted]

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

Summary tables for PASI scores and IGA mod 2011 categories will be imputed using MI.

Inferential analysis of percentage change in PASI score will be done using a mix-effects repeated measures model (MMRM) which is valid under the missing at random (MAR) assumption.

Missing data for ACR response variables will be handled based on a three tiered approach for drop-outs, complete missing data, and partial missing data.

1. Subjects who drop out of the trial for any reason will be considered non-responders from the time they drop out through week 52.
2. Subjects who do not have the required data to compute ACR response (i.e. tender and swollen joint counts and at least three of the five ACR core set variables) at baseline and at the specific time point will be classified as non-responders.

For subjects who switch treatment after induction period, values of induction period are not carried forward to maintenance period.

Following the intent-to-treat principle for subjects who prematurely discontinue treatment, but who are observed in the follow-up period, efficacy data collected in follow-up periods will be linked to planned but missed study visits as well.

[redacted]

Baseline values will not be carried forward.

9.4.4 Sensitivity analyses

Sensitivity analyses will be performed as follows:

PASI 75 and IGA mod 2011 0 or 1 response at Week 12 will be evaluated using an exact logistic regression model with non-responder imputations instead of multiple imputations for missing values.

[redacted]

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Maintenance of PASI 75 response after 52 weeks of treatment

Summary statistics as well as 95% confidence intervals will be presented for maintenance of PASI 75 response at Week 52 for the subset of subjects with PASI 75 response at Week 12 in the secukinumab treatment groups.

In addition, Kaplan-Meier estimates including 95% confidence intervals for cumulative rate of subjects losing PASI 75 response up to Week 52 will be calculated for the subset of subjects with PASI 75 response at Week 12 in the secukinumab treatment groups.

Maintenance of IGA 0 or 1 response after 52 weeks of treatment

The same analyses as planned for maintenance of PASI 75 response will be performed for IGA 0 or 1 response after 52 weeks of treatment, but analyses will be based on the subset of subjects with IGA 0 or 1 response at Week 12.

PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response over time

Summary statistics for PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response by visit will be presented in contingency tables and will include absolute and relative frequencies. Confidence intervals for response rates will be derived as well based on the score method including continuity correction (Newcombe 1998).

For PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response at each visit up to Week 12, each secukinumab dose regimen will be compared to placebo using an exact logistic regression model with treatment group, baseline body weight, geographical region, presence of psoriatic arthritis, and baseline PASI score as explanatory variables.

For PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response the placebo-adjusted response rates including 95% confidence interval will be derived by visit up to Week 12. In addition, Fisher's exact test will be applied to pairwise treatment group comparisons to placebo.

Figures will be provided as well displaying estimates for responder rates by treatment including confidence intervals.

PASI score over time

Summary statistics will be provided for absolute PASI scores as well as for percent change from baseline by visit and treatment group. Figures will also be provided.

The percentage change from baseline of PASI score at different time points will be analyzed via mixed model repeated measures (MMRM). Treatment group, visit, geographical region, presence of psoriatic arthritis and baseline PASI score will be fitted as continuous covariate. Treatment group by visit and visit by baseline PASI score will be included as interaction term in the model. An unstructured correlation matrix will be used thus allowing adjustment for correlations between time points within patients.

[redacted]

IGA mod 2011 score over time

Summary statistics for the IGA mod 2011 score over time will be presented by visit and treatment group in contingency tables.

Time to PASI 75 response

Number and percentage of subjects with PASI 75 response based on the number of subjects in the FAS at risk as denominator will be provided by treatment group.

Between-treatment differences will be evaluated using a log-rank test, stratified by geographical region, presence of psoriatic arthritis, to compare the cumulative rates between secukinumab treatment groups versus placebo. The hazard ratios for the comparisons and 95% confidence intervals will be computed using a stratified cox proportional hazards regression model with treatment and baseline PASI as explanatory variable and stratified by geographical region, presence of psoriatic arthritis.

Subjects without PASI 75 response will be considered as censored at Week 12.

[redacted]

Psoriatic arthritis

Summary statistics will be derived for [redacted] ACR 20 / 50 / 70 responses as well as for ACR component variables.

Relationship between response to secukinumab treatment and having failed to respond to previous biologic psoriasis therapy

Response variables PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 by visit will be tabulated versus previous systemic psoriasis therapy and response to previous biologic therapy, by treatment group.

[redacted]

9.5.2 Safety variables

All safety evaluations will be performed on the Safety set.

Adverse events

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

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

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

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

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

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

Laboratory data

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

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

In addition, shift tables will be provided for all lab parameters to compare a subject's baseline laboratory evaluation relative to the most extreme post-baseline laboratory test value. Shift tables with respect to Common Toxicity grade Criteria (CTC) and normal ranges will be provided by laboratory test and treatment group.

[redacted]

Vital signs

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed by vital sign and treatment group.

[redacted]

Change from baseline will only be summarized for subjects with both baseline and post-baseline values.

ECG

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

9.5.3 Resource utilization

Not applicable.

[redacted]

9.5.5 DNA

Not applicable.

9.5.6 Biomarkers

Not applicable.

[redacted]

9.7 Interim analyses

In addition to Week 16 analysis, additional subsequent interim analyses may be performed to fulfill any requests from Health Authorities. The treatment blinding after the Week 16 and any subsequent data base locks for interim analyses that may be requested by Health Authorities, is discussed in Section 5.3

9.8 Sample size calculation

This global study aims at complementing the safety and efficacy knowledge on secukinumab with data obtained from patients in China and other countries. The planned cohort sizes address this objective, in particular with respect to safety data.

At Baseline, subjects will be randomized to one of the two secukinumab treatment regimens or to placebo in a 2:1:1 ratio (300mg Secukinumab: 150mg Secukinumab: placebo). After the

[redacted]

first 12 weeks of treatment, non-responders under placebo will be re-assigned to 300 mg secukinumab treatment regimen.

Reported PASI 75 response rate to placebo is generally in the range of 3% to 7% (Papp 2006; Menter 2008; Leonardi 2008; Papp 2008) whilst in a recent phase III trial, observed PASI 75 response rate to placebo in Chinese subjects after twelve weeks of treatment was above 11% ("Safety and effectiveness of ustekinumab/stelara in Chinese patients with psoriasis", ClinicalTrials.gov Identifier: NCT01008995). It is estimated that in the present study, up to 10% of the subjects under placebo will achieve a PASI 75 response during the first twelve weeks of treatment (induction period).

According to CFDA requirement in use of biologic drug, it is planned to randomize 536 subjects at Baseline, i.e., using a 2:1:1 ratio, 268 patients for 300 mg secukinumab regimen and 134 patients for 150 mg secukinumab regimen and placebo group, respectively.

The PASI 75 and IGA mod 2011 0 or 1 response rates of secukinumab regimens at Week 12 are assessed based on Phase III trials. PASI 75 response rates at Week 12 are approximately 79.4% (95% C.I: [76.2, 82.4]) for the 300 mg secukinumab regimen and 69.2% (95% C.I: [65.6, 72.6]) for the 150 mg secukinumab regimen. IGA mod 2011 0 or 1 response rates at Week 12 are approximately 65.0% (95% C.I: [61.3, 68.6]) for the 300 mg secukinumab regimen and 51.4% (95% C.I: [47.7, 55.2]) for the 150 mg secukinumab regimen.

Since two secukinumab dose regimens will be tested in parallel versus placebo with respect to the co-primary endpoints, PASI 75 response and IGA mod 2011 0 or 1 response after 12 weeks of treatment, the type-I-error for each comparison will be split to $\alpha/2$ (family-wise α=2.5%, one-sided). With 536 (using a 2:1:1 ratio) subjects and assuming a response rate in the placebo group of 10% for PASI 75 response and IGA mod 2011 0 or 1 response, the power to demonstrate a response rate of 65.6% for PASI 75 and 47.7% for IGA mod 2011 0 or 1 in the secukinumab groups is above 99%, based on Fisher's exact test (nQuery Advisor 7.0, two group Fisher's-exact test of equal proportions).

The PASI 90 response rates of secukinumab regimens are approximately 56.6% (95% C.I: [52.8, 60.3]) for the 300 mg secukinumab regimen and 41.1% (95% C.I: [37.4, 44.9]) for the 150 mg secukinumab regimen.

With respect to the secondary endpoint of PASI 90 response at week 12 and with sample size of 536 (using a 2:1:1 ratio), the power to detect differences in response rates for each secukinumab dose regimen versus placebo is above 99%, based on Fisher's exact test with type-I-error of $\alpha/2$ (family-wise α=2.5%, one-sided) for each comparison and placebo response rate of 5%.

Table 9-1 Response reference for sample size calculation based on Phase III trials

Response at Week 12	AIN457 150 mg	AIN457 300 mg
IGA 0/1	(51.4) (47.7, 55.2)	(65.0) (61.3, 68.6)
PASI 75	(69.2) (65.6, 72.6)	(79.4) (76.2, 82.4)
PASI 90	(41.1) (37.4, 44.9)	(56.6) (52.8, 60.3)

[redacted]

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients/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 patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

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

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient 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 patients/subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

[redacted]

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

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

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

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

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/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 patients/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 patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

[redacted]

12 References

Alamanos Y, Voulgari PV, Drosos AA (2008) Incidence and Prevalence of Psoriatic Arthritis: A Systematic Review. J.Rheumatology; 35; 1354-1358.

Baek JH, Yoo CD, Shin KC et al. (2000) Spondylitis is the most common pattern of psoriatic artheritis in Korea. 19: 89-94.

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

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

Christophers E, Mrowietz U (2003) Psoriasis. In: Freedberg IM, Eisen AZ, Wolff K, et al (eds) Fitzpatrick's Dermatology In General Medicine. 6th ed; New York: McGraw-Hill: p.407-427

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

Dhir V, Aggarwal A (2013) Psoriatic Arthritis: a Critical Review. Clinic Rev Allerg Immunol; 44:141-148

Ding X, Wang T, Shen Y et al (2012) Prevalence of psoriasis in China: A population-based study in six cities. Eur J Dermatol; 22(5): 663-7.

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

Farber EM (1998) Juvenile psoriasis: Early interventions can reduce risks for problems later. Postgraduate Medicine; 103(4):89-100.

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

Fan X, Yang S, Sun LD et al. (2007) Coparison of Clinical Features of HLA-Cw*0602-Positive and Negative Psoriasis Patients in a Han Chinese Population. Acta Derm Venereol; 87: 335-340.

[redacted]

Gladmann DD, Antoni C, Mease P et al. (2005) Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis; 64 Suppl 2:ii 14-7.

Gottlieb AB, Griffiths CEM, Ho VC et al. (2005) Oral pimecrolimus in the treatment of moderate to severe Chronic plaque-type psoriasis: a double –blind, multicenter, randomized, dose-finding trail. British association of Dermatology; 152.1219-1217.

Griffiths CEM, Barker JNWN (2007) Pathogenesis and clinical features of psoriasis. Lancet; 370: 263 – 271.

[redacted]

Hukuda S, Minami M, Saito T et al. (2001) Spondyloarthropathies in Japan: nationwide questionnaire performed by the Japan Anklylosing Spondylitis Society. J Rheumatol; 28; 554-559.

Kawada A, Tezuka T, Nakamizo Y et al. (2003) A survey of psoriasis patients in Japan from 1982 to 2001. J. of Dermatological Science; 31, 59-64.

Kundakci N, Tursen U, Babiker MOA et al. (2002) The evaluation of the sociodemographic and clinical features of Turkish psoriasis patients. Intern Journal of Dermatology, 41:220-224.

Jamshidi F, Bouzari N, Seirafi H et al.(2008) The Prevalence of Psoriatic Arthrites in Psoriatic Patients in Tehran, Iran. Arch. Iranian Med ; 11(2) :162-165.

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

Leonradi C., Menter A., Hamilton T., Caro I., Xing B., Gottlieb AB. (2008) Efalizumab: results of a 3-year continuous dosing study for the long-term control of psoriasis Br J Dermatol. May; 158(5):1107-16. doi: 10.1111/j.1365-2133.2008.08548.x. Epub 2008 Mar 27

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

Mancia G, Backer GD, Dominiczak A et al. (2007) The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Journal of Hypertension ; 25: 1105-1187.

McInnes IB , Mease PJ, Kirkham B et al., (2015) Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE2): a randomized, double – blind, placebo-controlled, phase 3 trial. The Lancet; 386:1137- 1146.

Moll JMH and Wright V (1973) Psoriatic arthritis. Seminars in Arthritis and Rheumatism; 3(1): 55-78.

Naldi L (2004) Epidemiology of Psoriasis. Current Drug Targets- Inflammation and Allergy; (3) 2: 121-128

Newcombe RG (1998) Improved confidence intervals for the difference between binomial proportions based on paired data Stat Med. 1998 Nov 30; 17 (22):2635-50Oranje AP, Devillers AC, Kunz B, Jones SL, DeRaeve L, Van Gysel D, de Waard-van der Spek FB, Grimalt R, Torrelo A, Stevens J, Harper J. (2006) Treatment of patients with atopic dermatitis using wet-wrap dressings with diluted steroids and/or emollients. An expert panel's opinion and review of the literature J Eur Acad Dermatol Venereol. Nov; 20 (10):1277-86

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

Prasad P, Bikku B, Kaviarasan P K, Senthilnathan A. (2007) A clinical study of psoriatic arthropathy. Indian J Dermatol Venereol Leprol; 73:166-70

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

Rapp SR, Feldman SR, Exum ML, et al (1999) Psoriasis causes as much disability as other major medical diseases. J Am Acad Dematol; 41:401-7.

[redacted]

Schon MP and Henning Boehncke W (2005) Psoriasis. NEJM; 352; 18:1899-1912.

Taylor W, Gladman D, Helliwell P, et al. (2006); CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum; 54(8): 2665-73

Thumboo J, Tham SN, Tay YK, et al., (1997) Patterns of Psoriatic Artheritis in Orientals. J Rheumatol; 24:1949-53.

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

Zeng YQ, Chen R, Darmawan J et al. (2008) Rheumatic Diseases in China. Arthritis Research &Therapy; 10:R17

[redacted]

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 whether & which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the subject.

Liver Function and Related Variables

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

Renal Function and Electrolyte Variables

Creatinine (serum):	> 1.5 x ULN
Potassium:	> 6 mmol/L or < 3 mmol/L
Sodium:	> 160 mmol/L or < 115 mmol/L

Hematology Variables

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

Urinalysis Variable

Protein urine dipstick:	++*

* ++ is ≥ 100 mg/dL

14 Appendix 2: The classification criteria for psoriatic arthritis (CASPAR)

To meet the ClASsification of Psoriatic ARthritis (CASPAR) criteria for the diagnosis of psoriatic arthritis according to Taylor et al, 2006, a subject must cumulate at least 3 points from the following 5 categories:

1. Evidence of current psoriasis, or personal history of psoriasis, or family history of psoriasis:
   - Current psoriasis is defined as psoriatic skin or scalp disease present today, as judged by a rheumatologist or dermatologist (**2 points**).

[redacted]

- Personal history of psoriasis is defined as history of psoriasis that may be obtained from a patient, a family physician, dermatologist, rheumatologist, or other qualified health care provider (**1 point**, unless current psoriasis).
- Family history of psoriasis is defined as history of psoriasis in a first- or second-degree relative according to the subject (**1 point**, unless current psoriasis or personal history of psoriasis).

2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination **(1 point)**.
3. Negative test result for the presence of rheumatoid factor by any method except latex **(1 point)**.
4. Either current dactylitis, defined as swelling of an entire digit, or history of dactylitis recorded by a rheumatologist **(1 point)**.
5. Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (excluding osteophyte formation) on plain radiographs of the hand or the foot **(1 point)**.

Total score: _____

All study subjects are expected to have current psoriasis, thus 2 points should be recorded for question 1 of the assessment. Personal history of psoriasis and family history of psoriasis will be recorded in the Investigator Comments section of the CASPAR eCRF however these will not be taken into account for the subtotal score of question 1 and will not contribute to the total score calculated on the eCRF.

The CASPAR eCRF will populate automatically the total score cumulated by a subject. If the total score is ≥3, the subject meets CASPAR criteria.

[redacted]