NOVARTIS

Clinical Development – Medical Affairs Region Europe

[Cosentyx® (Secukinumab)]
Clinical Trial Protocol

[CAIN457A3302] / NCT02409667

OPTIMISE (OPtimization of Treatment In MaIntenance with SEcukinumab 300 mg)

[Long term clear skin maintenance treatment optimization in patients with moderate to severe chronic plaque psoriasis: A randomized, multicenter, open-label with blinded-assessment, comparative, 52 week study to evaluate the efficacy, safety and tolerability of secukinumab 300 mg s.c.]

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List of abbreviations

AE	Adverse Event
AIN457	Secukinumab
ALT (SGPT)	Alanine Aminotransferase
AST (SGOT)	Aspartate Aminotransferase
bpm	Beats per Minute
BSA	Body Surface Area
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	End of Treatment
EOT1	End of Treatment Period 1
EOT2	End of Treatment Period 2
EQ-5D	Health Status Questionnaire (EuroQOL 5-Dimension Health Questionnaire, EQ-5D©)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
H	Head [PASI scoring system]
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

[redacted]

IEC	Independent Ethics Committee
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011
IgG	Immunoglobulin G
IL	Interleukin
IUD	Intrauterine Device
IUS	Intrauterine System
IRB	Institutional Review Board
IRT	Interactive Response Technology
L	Lower limbs [PASI scoring system]
LFT	Liver Function Test
MedDRA	Medical Dictionary for Regulatory Activities
NR	Non Responder
NRS	Numeric Rating Scale
NYHA	New York Heart Association
PASI	Psoriasis Area and Severity Index
PFS	Pre-Filled Syringe
PR	Partial Responder
PRO	Patient Reported Outcomes
RAN	Retreatment as Needed
SAE	Serious Adverse Event
s.c.	Subcutaneous, subcutaneously
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Trunk [PASI scoring system]
TB	Tuberculosis
TCS	Topical Corticosteroid
TNF	Tumor Necrosis Factor
U	Upper limbs [PASI scoring system]
UNL	Upper Normal Limit
UV	Ultraviolet
WBC	White Blood Cells

[redacted]

WPAI-PSO	Work Productivity and Activity Impairment Questionnaire-Psoriasis

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained prior to starting any of the procedures described in the protocol.
Medication number	A unique identifier on the label of each study drug package in studies that dispense medication using an Interactive Response Technology (IRT) system.
Protocol	A written account of all the procedures to be followed in a study, which describes all the administrative, documentation, analytical and clinical processes used in the study.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned, unless the patient is followed for progression and/or survival.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment group assignment.
Study drug	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug(s), active drug run-ins, or background therapy.
Patient number	A number assigned to each patient who enrolls into the study.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study.

[redacted]

Amendment rationale

The main purpose of this Amendment is to align the requirements for the duration of contraception to be used by patients during the study with the approved European Summary of Product Characteristics. According to the Exclusion criteria (Section 4.2) of the study protocol women of childbearing potential must use effective methods of contraception during dosing of study treatment and for 16 weeks after stopping treatment, in line with phase III AIN457A program study protocols.

Therefore the advice to female patients to prevent pregnancy is amended to cover also the contraception length post treatment requirements of the European Summary of Product Characteristics (20 weeks).

In addition, the approved European Summary of Product Characteristics specifies for the pre-filled secukinumab syringe a warning and precaution for use in case a latex sensitivity would be pertinent for a patient. The removable needle cap of the pre-filled syringe contains a derivative of natural rubber latex; no natural rubber latex has to date been detected in the removable needle cap. Nevertheless, the use of pre-filled syringes in latex sensitive individuals has not been studied and there is therefore a potential risk of hypersensitivity reactions which cannot be completely ruled out. The Exclusion criteria (Section 4.2) of the study protocol have been updated accordingly, as well as the Risks and benefits (Section 3.6).

Other sections have been updated to provide clarity.

Changes to the protocol

The main changes made to the protocol are:

- Protocol synopsis: updated to reflect the changes in the main protocol text
- Section 4.2 exclusion criterion 3 and the Risks and benefits (Section 3.6) are revised to include also latex hypersensitivity
- Section 4.2 exclusion criterion 8 is revised to align post treatment contraception length with the EU Summary of Product Characteristics
- Section 6 updated content, incl. Table 6-1, to clarify details for the laboratory assessments, clarify that the 5 response level EQ-5D Health Status Questionnaire is used, and that Chest X-ray (or CT/MRI) is recorded on source documentation
- Section 6.2.5 is updated to include a statement on Crohn's disease

The first patient was recruited in the study on 12 June 2015 and around 11 of 1580 planned patients have been treated with study medication during finalization of the protocol amendment.

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

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

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

[redacted]

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

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Protocol summary

Protocol number	CAIN457A3302
Title	Long term clear skin maintenance treatment optimization in patients with moderate to severe chronic plaque psoriasis: A randomized, multicenter, open-label with blinded-assessment, comparative, 52 week study to evaluate the efficacy, safety and tolerability of secukinumab 300 mg s.c.
Brief title	Efficacy, safety and tolerability assessment of secukinumab 300 mg s.c. optimization in patients with moderate to severe chronic plaque psoriasis.
Sponsor and clinical phase	Novartis; Phase 3b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Reducing maintenance dosing regimens for patients treated with (biologic) drugs offers benefits, such as minimizing patients' exposure to the drug substance while keeping an acceptable clinical response. In contrast, patients not responding adequately to a drug substance can benefit from an increased frequency of drug dosing. In daily clinical practice, a change of the dose frequency for marketed substances can be assumed to happen often depending on the treatment response of patients. A secukinumab dose of 300 mg s.c. every 4 weeks as a maintenance treatment dose regimen has been evaluated extensively in a Phase 3 clinical trial program and shown strong sustainability of treatment response over 52 weeks. This study will assess if a more prolonged dose interval (every 6 weeks compared to every 4 weeks) will allow psoriasis patients who achieve clear or almost clear skin after 24 weeks of secukinumab treatment - Psoriasis Area and Severity Index (PASI) ≥ 90 - to maintain this skin response for a further 28 weeks (52 weeks in total). The study will also assess if a dose interval (dosing every 2 weeks compared to every 4 weeks) will allow psoriasis patients who fail to achieve a PASI 90 response after 24 weeks of secukinumab treatment to meet the PASI 90 response target in a further 28-week study period.
Primary Objective	The primary objective is to demonstrate in the patient pool of PASI 90 responders at Week 24 that secukinumab 300 mg s.c. every 6 weeks treatment is non-inferior to secukinumab 300 mg s.c. every 4 weeks treatment with respect to maintaining a PASI 90 response rate at Week 52.
Secondary Objectives	The key secondary objective is to demonstrate in the patient pool of PASI 75 responders who do not reach a PASI 90 response at Week 24 that secukinumab 300 mg s.c. administered every 2 weeks is superior to secukinumab 300 mg s.c. administered every 4 weeks at Week 52 based on the PASI 90 response rate. Other secondary objectives are as follows:

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	• Evaluate the proportion of PASI 50, PASI 75, PASI 100 and Novartis Investigator's Global Assessment modified 2011 (IGA mod 2011) 0/1 responder rates at Week 52. • Evaluate the course of mean PASI over time from Week 24 to Week 52. • Evaluate the effect of different maintenance treatment frequencies on patient reported outcomes (PROs): Dermatology Life Quality Index (DLQI©), EuroQOL 5-Dimension Health Questionnaire (EQ-5D©), Work Productivity and Activity Impairment Questionnaire-Psoriasis (WPAI-PSO), and the patient's assessment of pain, itching and scaling.
Exploratory objectives	Exploratory objectives are as follows: • Evaluate the proportion of PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1 responders at Week 24. • Evaluate the time to achieve clear or almost clear skin based on PASI 90 when receiving secukinumab 300 mg s.c. every 2 weeks compared to every 4 weeks from Week 24 to Week 52. • Evaluate time to first loss of PASI 75 response when receiving secukinumab every 2 weeks compared to every 4 weeks from Week 24 until Week 52. • Evaluate the safety and tolerability of different maintenance treatment regimens of secukinumab 300 mg s.c. • Explore the correlation between the pharmacokinetic (PK) data and efficacy outcomes. Other exploratory objectives for patients with PASI 90 response at Week 24 are as follows: • Assess the time to loss of PASI 90 response. • Assess the time to loss of IGA mod 2011 0/1 response.
Study design	This is a randomized, open-label, assessment-blinded, multicenter, 52-week study to evaluate the efficacy (based on PASI 90), safety and tolerability of secukinumab 300 mg s.c. in patients with moderate to severe chronic plaque psoriasis. This study consists of 2 treatment periods: a 24-week run-in treatment period (Baseline to Week 24) and a 28-week maintenance treatment period (Week 24 to Week 52). For Treatment Period 1 (Baseline to Week 24) all patients will receive the same treatment: 300 mg of secukinumab by s.c. injection with initial dosing at Weeks 0, 1, 2, and 3 followed by dosing every 4 weeks. For Treatment Period 2 (Week 24 to Week 52) patients will be randomly assigned to one of 4 treatment groups depending on their PASI response to treatment. Patients with PASI 90 (psoriasis clear or almost clear skin) will be randomized at Week 24 on a 1:1 basis to Group 1 or Group 2: • Group 1 (recommended maintenance treatment): secukinumab 300 mg s.c. every 4 weeks. • Group 2 (experimental dosing maintenance treatment): secukinumab 300 mg s.c. every 6 weeks. Patients who do not achieve a PASI 90 response at Week 24 but achieve at least a PASI 75 response will be eligible for dose frequency intensification and will be randomized on a 1:1 basis to either Group 3 or Group 4:

[redacted]

	• Group 3 (recommended maintenance treatment): secukinumab s.c. 300 mg every 4 weeks. • Group 4 (experimental maintenance treatment): secukinumab s.c. 300 mg every 2 weeks. Patients from Group 3 and Group 4 will enter a treatment-free follow-up period from Week 52 until Week 60. Patients without a PASI 75 response at Week 24 will not be eligible for randomization and will be discontinued from the study. Randomization will be stratified by body weight collected at the Randomization Visit (< 90 kg or ≥ 90 kg).
Population	The study population will consist of a representative group of male and female patients (≥ 18 years old) with moderate to severe chronic plaque psoriasis who are candidates for systemic treatment. Moderate to severe chronic plaque psoriasis is defined by a total PASI score of ≥ 10 and a body surface area (BSA) ≥ 10% approaching a described European consensus.
Inclusion criteria	Patients eligible for inclusion in this study have to fulfill **all** of the following criteria: 1. Men or women at least 18 years of age at the time of Screening. 2. Chronic plaque-type psoriasis diagnosed for at least 6 months prior to Screening and candidate for systemic therapy. 3. Moderate to severe psoriasis at Baseline as evidenced by: • PASI ≥ 10 *and* • IGA mod 2011 score of 3 or higher (based on a scale of 0 to 4) *and* • BSA affected by plaque-type psoriasis of ≥ 10%. 4. Patients 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 consent form (ICF) according to local laws and regulations.
Exclusion criteria	Patients fulfilling **any** of the following criteria will not be eligible for inclusion in this study. No additional exclusions may be applied by the Investigator in order to ensure that the study population is representative of all eligible patients. 1. History of exposure to any biologic drug taken for the treatment of chronic plaque psoriasis or any other indication including but not limited to anti-tumor necrosis factor (TNF) alpha, anti-interleukin (IL)12/23, or any anti-IL-17A or IL-17A receptor (IL-17AR) antibody. 2. Use of any other investigational drug within 4 weeks prior to Baseline or within a period of 5 half-lives of the investigational drug, whichever is longer. 3. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes including latex hypersensitivity. 4. Forms of psoriasis other than chronic plaque-type (eg, pustular, erythrodermic and guttate psoriasis). 5. Drug-induced psoriasis (ie, new onset or current exacerbation

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	from beta-blockers, calcium channel inhibitors or lithium). 6. Ongoing use of prohibited psoriasis treatments (eg, topical or systemic corticosteroids, ultraviolet (UV) therapy). 7. Ongoing use of other non-psoriasis prohibited treatments. Washout periods detailed in the protocol have to be adhered to. All other prior non-psoriasis concomitant treatments must be at a stable dose as detailed in the protocol before initiation of study drug. 8. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (> 5 mIU/mL). 9. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during entire study or longer if required by locally approved prescribing information (e.g. in EU 20 weeks). Effective contraception methods include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before taking study drug. • In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment. • Male sterilization (at least 6 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient. • Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository. • Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example, hormone vaginal ring or transdermal hormone contraception. • Placement of an intrauterine device (IUD) or intrauterine system (IUS). • In case of use of oral contraception women should have been stable on the same pill for a minimum of 12 weeks before taking study drug. 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 (eg, age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of

[redacted]

	the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential. 10. Active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of secukinumab therapy. 11. Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions) which, in the opinion of the Investigator, significantly immunocompromises the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy. 12. Investigator discretion should be used for patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders. 13. Significant medical problems, including but not limited to the following: uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg), congestive heart failure (New York Heart Association [NYHA] status of class III or IV). 14. Serum creatinine level exceeding 2.0 mg/dL (176.8 µmol/L) at Screening. 15. Total white blood cell (WBC) count < 2500/µL, platelets < 100 000/µL, neutrophils < 1500/µL or hemoglobin < 8.5 g/dL, at Screening. 16. Active systemic infections during the 2 weeks prior to Baseline (exception: common cold) or any infection that reoccurs on a regular basis. 17. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis (TB) infection as defined by a positive QuantiFERON TB-Gold test (QFT) at Screening. Patients with a positive or indeterminate QFT test may participate in the study if full TB work-up (according to local practice/guidelines) completed within 12 weeks prior to Day 1 (Baseline) establishes conclusively that the patient has no evidence of active TB. If presence of latent TB is established, then treatment must have been initiated and maintained according to local country guidelines prior to Day 1 (Baseline). 18. Chest X-ray, computerized tomography (CT) scan, or magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process, obtained within 12 weeks prior to Baseline, and evaluated by a qualified physician. 19. Past medical history record of, or current infection with, human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus prior to Baseline. 20. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for skin Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed). 21. Current severe progressive or uncontrolled disease which in the judgment of the Investigator renders the patient unsuitable for the study or puts the patient at increased risk (eg, myocardial

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	infarction within 26 weeks prior to Baseline). 22. Inability or unwillingness to undergo repeated venipuncture (eg, because of poor tolerability or lack of access to veins). 23. Any medical or psychiatric condition which, in the Investigator's opinion, would preclude the patient from adhering to the protocol or completing the study per protocol. 24. History or evidence of ongoing alcohol or drug abuse within the last 6 months prior to Baseline. 25. Plans for administration of live vaccines during the study period or in the 6 weeks prior to Baseline. 26. Not willing to limit UV light exposure (eg, sunbathing and/or the use of tanning devices) during the course of the study.
Investigational and reference therapy	Secukinumab 150 mg will be provided in 1 mL prefilled syringes (PFS) for s.c. injection. Secukinumab 300 mg (2 × PFS of the 150 mg dose) will be self-administered by the patient. The study drug supplies will be open label. Treatment period 1 (Baseline to Week 24): • Secukinumab 300 mg s.c. will be self-administered at Baseline, once weekly at Weeks 1, 2 and 3, and thereafter every 4 weeks, starting from Week 4 (ie, Week 4, 8, 12, 16 and 20). Treatment period 2 (Week 24 to Week 52): At Week 24, patients with at least PASI 90 response will be randomly assigned on a 1:1 basis to Group 1 or Group 2 as follows: • Group 1: secukinumab 300 mg s.c. every 4 weeks (Week 24, 28, 32, 36, 40, 44 and 48). • Group 2: secukinumab 300 mg s.c. every 6 weeks (Week 24, 30, 36, 42 and 48). At Week 24, patients with a PASI response of 75 but not PASI 90 will be randomly assigned on a 1:1 basis to Group 3 or Group 4 as follows: • Group 3: secukinumab 300 mg s.c. every 4 weeks (Week 24, 28, 32, 36, 40, 44 and 48). • Group 4: secukinumab 300 mg s.c. every 2 weeks (Week 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 48).
Efficacy assessments	The following assessments will be performed: • IGA mod 2011 • PASI Patient related outcomes (PRO) will be assessed using the following health related quality of life (HRQoL) assessments: • DLQI© • Patient's assessment of pain, itching and scaling • EQ-5D© • WPAI-PSO
Safety assessments	Safety will be assessed via the monitoring of physical examinations, vital signs, routine laboratory (clinical chemistry including urinalysis and hematology) data and adverse events (AEs).
Other assessments	The correlation between pharmacokinetic (PK) data and efficacy outcomes will also be assessed.

[redacted]

Data analysis	The Full Analysis Set for Treatment Period 2 of PASI 90 Responders (FAS-P90R) will include all patients who are rated as PASI 90 responders at Week 24, are randomized to treatment Group 1 or Group 2, and who received at least one dose of study drug at- or after Week 24. The primary variable is the maintenance of the PASI 90 response rate at Week 52 in the FAS-P90R, ie the rate of patients who maintain their PASI 90 response assessed at Week 24 also at Week 52. The aim of the primary analysis for this study will be to demonstrate the non-inferiority of the 6-weekly dosing group compared to the 4-weekly dosing group, with respect to the primary endpoint in the FAS-P90R. The primary analysis will be performed comparing dosing groups (Group 1 vs Group 2) with respect to the primary efficacy variable in a logistic regression model with the factors treatment, country, body weight (< 90 kg or ≥ 90 kg), and PASI 90 response (Y/N) at Week 16. The odds ratio with its corresponding 95% confidence interval (CI) will be given (please notice that the upper limit of a 2-sided 95% CI is identical to the upper limit of a 1-sided 97.5% CI, which would correspond to a 1-sided test with a significance level of 2.5%). Additionally, a (1-sided) p-value for the shifted null-hypothesis will be computed. The key secondary variable is the PASI 90 response rate at Week 52 in the FAS-P75P, ie, the proportion of patients with a PASI 75 response but also less than a PASI 90 response at Week 24 who achieve a PASI 90 response at Week 52. The key secondary analysis of this study will be to demonstrate superiority of the shortened 2-weekly dosing group compared to the 4-weekly dosing group in the FAS-P75P. This analysis will be performed comparing dosing groups (Group 3 vs Group 4) with respect to the key secondary variable in a logistic regression model with the factors treatment, country and PASI response (75% to 82% or 83% to 89%) at Week 24. The odds ratio with its corresponding 95% CI and p-value will be presented. The key secondary analysis will be included in a confirmatory testing strategy. For the safety evaluation, the patient groups of i/ PASI 90 responders and ii/ PASI 75 but not PASI 90 responders will be pooled; therefore, only 3 groups will be compared: • secukinumab 300 mg s.c. every 2 weeks (patients from Group 4). • secukinumab 300 mg s.c. every 4 weeks (patients from Group 1 pooled with Group 3). • secukinumab 300 mg s.c. every 6 weeks (patients from Group 2). Patients will be analyzed according to the treatment they received. Treatment emergent AEs will be summarized by system organ class (SOC) and preferred term.
Key words	Open-label, randomized, blinded assessment, chronic plaque psoriasis, PASI, secukinumab, monoclonal antibody

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1 Introduction

1.1 Background

Psoriasis is a chronic, immune-mediated inflammatory disease that affects up to 3% of the population worldwide (Jacobson et al 2011). Psoriasis typically manifests as plaques (Lebwohl 2003) that occur most commonly on the skin of the elbows and knees. Plaques can affect any area, including the palms and soles (Pettey et al 2003); fingernails and toenails are also commonly affected (Radtke et al 2011). The efficacy of systemic therapy with biologics in the treatment of moderate-to-severe plaque psoriasis is well established (Christophers et al 2013; Herrier 2011).

Secukinumab is a fully human immunoglobulin G1/κ-class (IgG) anti-interleukin (IL)-17A monoclonal antibody that selectively suppresses the inflammatory cascade induced by the cytokine IL-17A. Secukinumab has demonstrated efficacy and safety for the treatment of moderate-to-severe plaque psoriasis (Langley et al 2014; Paul et al 2014). A large proportion of patients (71%) with moderate to severe plaque psoriasis achieved a Psoriasis Area and Severity Index (PASI) 90 response after 16 weeks of treatment with secukinumab 300 mg s.c. Subcutaneous injections were administered every 4 weeks with the exception of the first 4 weeks of treatment when the drug was given weekly. A sustainable drug response was still evidenced at Week 52 with a PASI 90 response rate of 63%. The Investigator Global Assessment modified 2011 (IGA mod 2011; Langley et al 2013) 0/1 response rate was comparable to the PASI 90 response with approximately 74% and 64% of patients achieving a clinical response at Week 16 and Week 52, respectively (pooled data from CAIN4572302 and CAIN4572303 pivotal studies). The Phase 3 clinical trials data support the use of secukinumab 300 mg s.c. every 4 weeks for maintenance of clinical response.

Optimizing maintenance dosing regimens for patients treated with (biologic) drugs offers many benefits, such as minimizing patients' exposure to the drug substance, increasing drug compliance and lessening economic burdens while keeping an acceptable clinical response. This principle has been investigated in a number of studies mainly in rheumatic disorders with currently available biological drugs. One psoriatic arthritis study demonstrated that most patients maintained their initial clinical response when the maintenance dose interval was prolonged from 2 weeks to 4 weeks after an initial induction period (Cantini et al 2012). Similar dose reductions have been reported in rheumatoid arthritis (den Broeder et al 2002) and in ankylosing spondylitis patients (Lee SH et al 2008). In these studies the original dosing interval was maintained but the dose was reduced. Dermatologists, like rheumatologists, are looking for a similar reduction and optimization in drug exposure once a patient has cleared, or almost cleared, skin from psoriasis. However, only one double-blind study investigating dose reduction of a biologic drug in psoriasis was identified in the literature which showed that the initial clinical response was maintained despite reducing the dose by 50% after 12 weeks (Papp et al 2005).

In contrast, patients not responding adequately to a biologic treatment can benefit from an increased frequency of drug dosing. Shortening dose intervals (off-label use) for marketed substances can be assumed to happen frequently especially in partial responders in daily practice. One study described that reducing the dosing interval (of ustekinumab) from 12 weeks to 8 weeks in partial responders had a good clinical effect (Kimball et al 2012).

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Similarly, another study demonstrated that shortening the dose interval (of adalimumab) from 2 weeks to 1 week was effective in patients who were refractory to both non-biological and biological treatment (Papoutsaki et al 2007).

At the present time clinical studies assessing flexible dosing regimens for long-term secukinumab treatment are very rare. A retreatment-as-needed (RAN) approach (ie, retreatment at start of relapse) has been assessed as an alternative to maintain response in some patients while adjusting drug exposure. The SCULPTURE (CAIN457A2304) study compared secukinumab RAN to a fixed-interval regimen (every 4 weeks) for the maintenance of efficacy up to 52 weeks in patients who achieved a PASI 75 response at Week 12 with secukinumab. The SCULPTURE study did not confirm the RAN dosing regimen as non-inferior to a fixed interval dosing regimen of secukinumab in plaque-type psoriasis even though both regimens led to clinically meaningful response rates. The fixed-dose interval regimen was shown to have clear benefits compared to the RAN regimen for sustained efficacy in the treatment of psoriasis (Mrowietz et al 2013). Consistently across efficacy measures, patients in the fixed-interval groups showed increased maintenance of response over those in the RAN groups. These results indicate that fixed-dose interval regimens are preferable over RAN regimens for maintenance dose regimens of secukinumab. Varying the duration of the fixed-dose interval of secukinumab in the maintenance period could potentially allow a better alternate approach for flexible dosing than the RAN approach and this will be investigated in the current study.

1.2 Purpose

The primary purpose of this study is to assess the efficacy and safety of different maintenance dosing regimens in patients who have achieved a PASI 90 response after 24 weeks of treatment with secukinumab 300 mg s.c. The current study will assess if an extended dose interval (every 6 weeks vs every 4 weeks) will allow psoriasis patients who achieve PASI 90 after 24 weeks of secukinumab treatment to maintain this response for a further 28 weeks (52 weeks in total).

The study will also assess whether dose intensification through a shortened dose interval (every 2 weeks vs every 4 weeks) will allow patients who are PASI 75 responders but not PASI 90 responders after 24 weeks of treatment with secukinumab 300 mg s.c. to achieve the PASI 90 target after a further 28 weeks of treatment in the maintenance period. In addition, patient reported outcomes (PRO) data will be collected to explore the effect of secukinumab on health-related quality of life (HRQoL) and work productivity.

2 Study objectives

2.1 Primary objective

The primary objective is to demonstrate in the patient pool of PASI 90 responders at Week 24 that secukinumab 300 mg s.c. every 6 weeks treatment is non-inferior to secukinumab 300 mg s.c. every 4 weeks treatment with respect to maintaining a PASI 90 response rate at Week 52.

2.2 Secondary objectives

The key secondary objective is to demonstrate in the patient pool of PASI 75 responders who do not reach a PASI 90 response at Week 24 that secukinumab 300 mg s.c. administered

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every 2 weeks is superior to secukinumab 300 mg s.c. administered every 4 weeks at Week 52 based on the PASI 90 response rate.

Other secondary objectives are as follows:

- Evaluate the proportion of PASI 50, PASI 75, PASI 100 and IGA mod 2011 0/1 responder rates at Week 52.
- Evaluate the course of mean PASI over time from Week 24 to Week 52.
- Evaluate the effect of different maintenance treatment frequencies on PROs: Dermatology Life Quality Index (DLQI), EuroQOL 5-Dimension Health Questionnaire (EQ-5D©), Work Productivity and Activity Impairment Questionnaire-Psoriasis (WPAI-PSO), and the patient's assessment of pain, itching and scaling.

2.3 Exploratory objectives

- Evaluate the proportion of PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1 responders at Week 24.
- Evaluate the time to achieve clear or almost clear skin based on PASI 90 when receiving secukinumab 300 mg s.c. every 2 weeks compared to every 4 weeks from Week 24 to Week 52.
- Evaluate time to first loss of PASI 75 response when receiving secukinumab every 2 weeks compared to every 4 weeks from Week 24 until Week 52.
- Evaluate the safety and tolerability of different maintenance treatment regimens of secukinumab 300 mg s.c.
- Explore the correlation between the pharmacokinetic (PK) data and efficacy outcomes.

Other exploratory objectives for patients with PASI 90 response at Week 24 are as follows:

- Assess the time to loss of PASI 90 response.
- Assess the time to loss of IGA mod 2011 0/1 response.

3 Investigational plan

3.1 Study design

This is a randomized, open-label with blinded-assessment, multicenter, 52-week study to evaluate the efficacy (based on PASI 90), safety and tolerability of secukinumab 300 mg s.c. in patients with moderate to severe chronic plaque psoriasis. This study consists of 2 treatment periods: a 24-week run-in treatment period (Baseline to Week 24) and a 28-week maintenance treatment period (Week 24 to Week 52) as indicated in Figure 3-1.

[redacted]

For Treatment Period 1 (Baseline to Week 24) all patients will receive the same treatment:

- Secukinumab 300 mg s.c. will be self-administered at Baseline, once weekly at Week 1, 2 and 3; and thereafter every 4 weeks starting from Week 4 (ie, Week 4, 8, 12, 16 and 20).

At Week 24, all patients will be assessed in term of PASI response and either randomized to one of the 4 treatment groups in Treatment Period 2 (Week 24 to Week 52) or withdrawn from the study.

Patients with at least a 90% reduction in PASI score from Baseline will be randomized at Week 24 on a 1:1 basis to Group 1 or Group 2:

- Group 1 (recommended maintenance treatment): secukinumab 300 mg s.c. every 4 weeks (Week 24, 28, 32, 36, 40, 44 and 48).
- Group 2 (experimental dosing maintenance treatment): secukinumab 300 mg s.c. every 6 weeks (Week 24, 30, 36, 42 and 48).

Patients with less than 90% reduction in PASI score from Baseline at Week 24 but who achieved at least a 75% reduction in PASI score from Baseline are eligible for dose frequency intensification and will be randomized on a 1:1 basis to either Group 3 or Group 4:

- Group 3 (recommended maintenance treatment): secukinumab s.c. 300 mg every 4 weeks (Week 24, 28, 32, 36, 40, 44 and 48).
- Group 4 (experimental maintenance treatment): secukinumab s.c. 300 mg every 2 weeks (Week 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 48).

At Week 52, patients from Group 3 and Group 4 will enter into a treatment-free follow-up period until Week 60. From the last study drug administration at Week 48 to Week 60 (12 weeks) patients will not be allowed to take any study drug. At the Week 60 visit, relapse, rebound and safety will be explored.

At Week 24, patients with a reduction in PASI score from Baseline of less than 75% will not be eligible for randomization and will be discontinued from the study.

Randomization will be stratified by body weight collected at the Randomization Visit (< 90 kg or ≥ 90 kg).

The study drug will be self-administered by patients throughout the study. Study drug administration will occur at the study center for all study visits in Treatment Period 1; and at the study center or at the patient's home in Treatment Period 2. Self-administrations at every study center visit should be supervised by the study center personnel to ensure a correct study drug application and proper preparation of the patient for the home administration without study center personal supervision. If needed a caregiver of the patient can be trained for home administration to provide support. Home drug administration using the same injection device (ie, pre-filled syringes [PFS]) was introduced in previous secukinumab Phase 3b clinical studies, eg the CAIN457A2312, CAIN457A2313, and CAIN457A3301 studies. To allow for comparable treatment group data at fixed study visits, patients will be trained for home drug administration prior to Treatment Period 2.

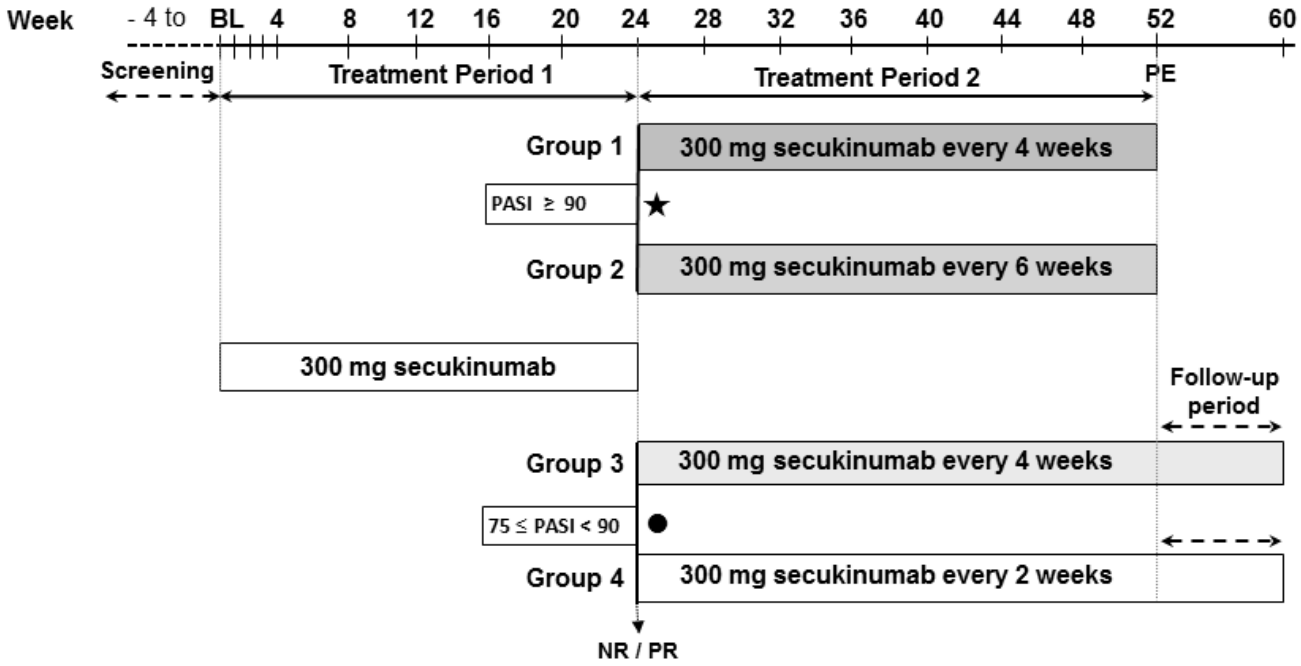
A blinded PASI assessor who has no access to the randomization details must perform all PASI and IGA mod 2011 efficacy assessments for Treatment Period 2 (Week 24 to Week 52). To reduce measurement variability it is recommended that the same blinded PASI assessor performs all PASI and IGA mod 2011 assessments for a single patient.

[redacted]

The blinded PASI assessor must not participate in any study-related activities that could compromise the blinding and should solely concentrate on the skin examination for PASI and IGA mod 2011 assessments. For more details please refer to Section 5.4.

Safety will be assessed throughout the study through the monitoring of AEs, SAEs, electrocardiograms (ECGs), vital signs and laboratory data.

Figure 3-1 Study design



★ randomization of responder (PASI ≥ 90)
● randomization of responder (75 ≤ PASI < 90)
BL: baseline
NR: non-responder (PASI < 50)
PE: primary endpoint
PR: partial responder (50 ≤ PASI < 75)

[redacted]

3.2 Rationale of study design

The secukinumab 300 mg s.c. every 4 weeks dose regimen has been evaluated extensively in a Phase 3 clinical trial program and showed strong sustainability of efficacy response with a good safety profile up to 52 weeks of treatment. Further knowledge for long term maintenance treatment flexibility for the optimal effective dose is a medical need that dermatologists are looking for with any biologic psoriasis drug in order to administer to the patient the right dose and regimen at the right treatment time.

The main reason for choosing the study design is to research in optimized maintenance treatment options to minimize drug exposure for secukinumab in patients cleared or almost cleared (PASI 90) from psoriasis while maintaining an acceptable clinical response and comparable safety profile.

Another reason for the study design is to examine if PASI 75 responders could benefit in terms of efficacy from an increased dosing interval for the study drug with a comparable safety profile. In the CAIN457A2212 study psoriasis patients have been exposed to an increased drug exposure without detection of any safety-related signals.

Taken together the rationale for the study is to explore options for individualizing maintenance treatment.

The CAIN457A2304 study, part of the secukinumab Phase 3 program, has assessed a RAN (retreatment at the start of relapse) approach as an alternative to maintain treatment response in some patients when secukinumab response has been achieved after 12 weeks. The fixed-dose interval regimen every 4 weeks was shown to have a clear benefit compared to the RAN regimen for sustained efficacy in the treatment of psoriasis (Mrowietz et al 2013).

At the present time, there is still a need for clinical study designs assessing flexible dosing options for long-term biologic treatment of psoriasis for patients who have achieved clear or almost clear skin under treatment, and additionally, when a certain drug response is achieved that could be optimized towards complete clearance of the symptoms. This more individualized maintenance treatment has become a treatment option to assess for secukinumab 300 mg s.c. since it has shown speed, strength and sustainability with 74.3% of biologic naïve psoriasis patients achieving PASI 90 at Week 24. At Week 52, 81.8% of the patients who achieved PASI 90 at Week 24 maintained clear or almost clear skin from psoriasis showing a high level of treatment sustainability in the maintenance period. Pooled data from the Phase 3 studies showed that 87.6% of biologic-naïve patients achieved at least the PASI 75 criterion at Week 24 (95% confidence interval (CI) ranged from 84.7% to 90.1%) and could therefore be regarded as responders to secukinumab. At Week 24, 5.9% of patients achieved a PASI 50 partial response but no PASI 75 response and therefore did not fully benefit from secukinumab, while 6.5% of patients were non-responders.

This study is designed to assess the primary objective of allowing more treatment flexibility (extended dose interval to every 6 weeks) with less drug exposure in moderate to severe psoriasis patients who achieved a PASI 90 response after 24 weeks of secukinumab 300 mg s.c. Furthermore, this study is designed to assess the key secondary objective of allowing more treatment flexibility (shortened treatment interval to 2 weeks) in moderate to severe psoriasis patients who achieved a PASI 75 but not a PASI 90 response after 24 weeks of secukinumab 300 mg s.c. every 4 weeks. The study will also evaluate the safety and

[redacted]

tolerability of secukinumab. In addition, the study will collect data on PROs to explore the effect of secukinumab 300 mg s.c. maintenance treatment on patient's health related quality of life and work productivity.

In this study, only secukinumab verum injections will be administered. This will more closely reflect a real-life situation for patients than, for example, using a double-blinded, double dummy study design that would require secukinumab placebo injections. The blinded assessor approach is enabling to capture cogent efficacy data deriving from Investigator assessments. In addition, the design supports for interpreting these Investigator assessments in the context of a patient's daily life and social function measured by PROs (EMEA/CHMP/EWP/139391/2004).

The treatment-free follow-up period will be limited to treatment Group 3 and Group 4 as treatment-free follow-up period data for drug exposures up to 300 mg s.c. every 4 weeks in the maintenance phase have already been extensively reported for the Phase 3 secukinumab program studies.

Rationale for choice of non-inferiority margin and primary endpoint

Statistical projections to support the choice of non-inferiority margin for this study are difficult as Week 24 to Week 52 data are not available for PASI 90 response rates in patients treated with the experimental dosing frequencies scheduled for this study. However, for the active controlled study CAIN457A2304 in the secukinumab development program the non-inferiority margin was set to 15%. Based on clinical judgment, a non-inferiority margin of 15% is justifiable also, especially when taking into account the maintenance phase endpoint and the maintenance responder rate (ie, 81.8% of patients achieving a PASI 90 response at Week 24 are still PASI 90 responders at Week 52) observed in the clinical trial program with secukinumab 300 mg s.c. to date. This non-inferiority margin has been accepted for the CAIN4572304 study by participating regulatory agencies in the US, EU and Japan.

Similar study designs for drug exposure reduction for other biologic treatments in moderate to severe psoriasis patients are very limited. In the rheumatoid arthritis indication, non-inferiority margins in studies with drug exposure reductions have been recently accepted up to a 20% non-inferiority margin for efficacy endpoints (den Broeder et al 2013, Mariette et al 2014).

The non-inferiority margin for the primary endpoint is also comparable to other efficacy endpoints of the mentioned studies and is considered a clinically balanced choice taking into account the likelihood to maintain a PASI 90 response rate in the study population treated with a prolonged dosing regimen (secukinumab Phase 3 program, pooled data of biologic naïve patients). It should be noted in this context that the PASI scoring system, even if used as one of the most frequent ones to assess psoriasis drug efficacy in clinical trials, is known to be complex and a certain measurement system variability applies (Costa de Faria et al 2010).

Sample size details are provided in Section 9.7.

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

The efficacy and safety of secukinumab 300 mg s.c. for the treatment of moderate-to-severe plaque psoriasis have been demonstrated in the Phase 3 clinical trial program. The 300 mg s.c. dose of secukinumab delivered the most clinically meaningful benefit to patients compared to

[redacted]

the 150 mg s.c. dose across all pivotal studies for all time points (Week 12 to Week 52) as described in Section 1. Therefore, a maintenance dose of 300 mg s.c. has been selected for all treatment groups proposed for this study. The dose interval for the initial treatment period (ie, once every week for the first 4 weeks, followed by once every 4 weeks until Week 24) has been selected as the Phase 3 clinical trial program demonstrated a strong efficacy response to treatment at this dose interval.

A more prolonged maintenance dose interval (every 6 weeks for Group 2) has been selected for patients who achieve clear or almost clear skin from psoriasis after 24 weeks of treatment (PASI $\geq$ 90) in order to establish if this dose interval is non-inferior to the current proven maintenance dose interval (ie, every 4 weeks), which is selected as the comparator group in this study.

A shortened dose interval (every 2 weeks) has been selected for Group 4 for patients who are responders but fail to achieve a response of PASI $\geq$ 90 after 24 weeks to establish if this dose interval is superior to the current proven maintenance dose interval (every 4 weeks) and to assess if this dose interval would allow patients to achieve the target response of PASI $\geq$ 90 after a further 28 weeks of treatment.

Although secukinumab 300 mg s.c. every 2 weeks has not been tested yet in a maintenance treatment period, no safety concerns are expected with this dose regimen based on the secukinumab results reported in the clinical trial program to date (Papp et al 2011). A 24-week initial treatment period (Baseline to randomization at Week 24) has been selected as the Phase 3 clinical trial program demonstrated a strong response to treatment. A 28-week maintenance treatment period (Week 24 to Week 52) has been selected as the Phase 3 clinical trial program demonstrated a sustainable high efficacy response for secukinumab 300 mg s.c. starting at Week 16 and remaining very stable until at least Week 24 under treatment (Langley et al 2014).

Randomization will be stratified by body weight collected at the Randomization Visit (< 90 kg or $\geq$ 90kg) to exclude corresponding imbalances in any patient group of this study. The same threshold split (90 kg) was used for the discourse with the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) and was studied extensively in the secukinumab Phase 3 program.

Pre-filled syringes have been selected for secukinumab s.c. administration in this study as these have been successfully used by patients in the Phase 3 clinical studies, which showed the use of PFS was safe and well tolerated. Self-injection with the PFS, following the utilized instructions for use, showed no significant safety hazards and was found to be acceptable to study participants and to the competent authorities for other secukinumab studies (CAIN457A2312, CAIN4572312 and CAIN457A3301).

3.4 Rationale for choice of comparator

This study was designed primarily to demonstrate the non-inferiority of secukinumab 300 mg s.c. every 6 weeks compared to secukinumab 300 mg s.c. every 4 weeks when administered as a maintenance treatment. Therefore, no placebo or other comparator treatment will be included in the study.

[redacted]

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

An extensive Phase 3 program demonstrated secukinumab to be very effective in treating plaque psoriasis, with 300 mg s.c. being the dose that delivered the most clinically meaningful benefit to patients with respect to achievement of almost clear to clear skin, improved quality of life (QoL), speed of onset of action, and sustainability of symptom relief. The majority of patients treated with this dose achieved clear to almost clear skin, as shown by PASI 90 response and IGA mod 2011 0/1 response, with a corresponding increase in DLQI response (Langley et al 2014; Paul et al 2014).

Secukinumab was generally safe and well-tolerated. The most frequently reported AEs were infections, especially upper respiratory tract infections with secukinumab relative to placebo. Related to the known mode of action, there was an increase in mucosal or cutaneous candidiasis infection with secukinumab compared to placebo, but the cases were generally mild or moderate in severity, non-serious, easily manageable, and responsive to standard treatment and did not lead to study discontinuation.

There was a small increase in mild to moderate neutropenia cases with secukinumab compared to placebo. Common Toxicity Criteria for AE grade 3 neutropenia (< 1.0 to 0.5 × 10^9/L) was uncommonly observed with secukinumab, most cases were transient and reversible without a temporal relationship to infections.

Hypersensitivity reactions including urticaria and one case of anaphylactic reaction to secukinumab were also observed in clinical studies. The removable needle cap of the pre-filled syringe contains a derivative of natural rubber latex; no natural rubber latex has to date been detected in the removable needle cap. Nevertheless, the use of pre-filled syringes in latex sensitive individuals has not been studied and there is therefore a potential risk of hypersensitivity reactions which cannot be completely ruled out.

Taking into account the individual risks as outlined above, the expected risk profile of secukinumab from a mechanism of action perspective is anticipated to be similar or improved compared to the approved inflammatory cytokine-targeting therapies. The risk to patients in this study will be minimized by compliance with the eligibility criteria, close clinical monitoring and extensive guidance to the Investigators provided in the current version of the Investigator's Brochure.

From the standpoint of the overall risk-benefit assessment, the current study with secukinumab is justified.

[redacted]

4 Population

The study population will consist of a representative group of male and female patients (≥ 18 years old) with moderate to severe chronic plaque psoriasis and candidates for systemic treatment. Moderate to severe chronic plaque psoriasis is defined by a total PASI score of ≥ 10 and a body surface area (BSA) of ≥ 10% approaching a described European consensus (Mrowietz et al 2011).

It is planned that approximately 2257 patients will be screened and around 1580 patients will be enrolled at Baseline to randomize 570 patients at Week 24 each for Group 1 and Group 2 (relevant groups for primary objective). Sample size details are provided in Section 9.7. Patients who drop out after they have been randomized will not be replaced. If a patient fails to be enrolled at Baseline, the patient may be rescreened if it can be assumed that the cause of Screening failure is only a temporary constraint. Patients may be screened more than once.

Randomization will be stratified by body weight at Week 24 (randomization visit). The strata will be "body weight ≥ 90 kg" or "body weight < 90 kg" for all treatment groups.

4.1 Inclusion criteria

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

1. Men or women at least 18 years of age at the time of Screening.
2. Chronic plaque-type psoriasis diagnosed for at least 6 months prior to Screening and candidate for systemic therapy.
3. Moderate to severe psoriasis at Baseline as evidenced by:
   - PASI ≥ 10 *and*
   - IGA mod 2011 score of 3 or higher (based on a scale of 0 to 4) *and*
   - BSA affected by plaque-type psoriasis of ≥ 10%
4. Patients 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 ICF according to local laws and regulations.

[redacted]

4.2 Exclusion criteria

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

1. History of exposure to any biologic drug taken for the treatment of chronic plaque psoriasis or any other indication including but not limited to anti-tumor necrosis factor (TNF) alpha, anti-IL12/23, or any anti-IL-17A or IL-17A receptor (IL-17AR) antibody.
2. Use of any other investigational drug within 4 weeks prior to Baseline or within a period of 5 half-lives of the investigational drug, whichever is longer.
3. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes including latex hypersensitivity.
4. Forms of psoriasis other than chronic plaque-type (eg, pustular, erythrodermic and guttate psoriasis).
5. Drug-induced psoriasis (ie, new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium).
6. Ongoing use of prohibited psoriasis treatments (eg, topical or systemic corticosteroids, ultraviolet (UV) therapy).
7. Ongoing use of other non-psoriasis prohibited treatments. Washout periods detailed in the protocol (Table 5-2) have to be adhered to. All other prior non-psoriasis concomitant treatments must be at a stable dose as detailed in the protocol before initiation of study drug.
8. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (> 5 mIU/mL).
9. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during entire study or longer if required by locally approved prescribing information (e.g. in EU 20 weeks). Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before taking study drug.
    - In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
    - Male sterilization (at least 6 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example, hormone vaginal ring or transdermal hormone contraception.
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS).

[redacted]

- 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 drug.

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 (eg, age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.

10. Active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of secukinumab therapy.
11. Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions) which, in the opinion of the Investigator, significantly immunocompromises the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy.
12. Investigator discretion should be used for patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders.
13. Significant medical problems, including but not limited to the following: uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg), congestive heart failure (New York Heart Association [NYHA] status of class III or IV).
14. Serum creatinine level exceeding 2.0 mg/dL (176.8 µmol/L) at Screening.
15. Total white blood cell (WBC) count < 2500/µL, platelets < 100 000/µL, neutrophils < 1500/µL or hemoglobin < 8.5 g/dL, at Screening.
16. Active systemic infections during the 2 weeks prior to Baseline (exception: common cold) or any infection that reoccurs on a regular basis.
17. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis (TB) infection as defined by a positive QuantiFERON TB-Gold test (QFT) at Screening. Patients with a positive or indeterminate QFT test may participate in the study if full TB work-up (according to local practice/guidelines) completed within 12 weeks prior to Day 1 (Baseline) establishes conclusively that the patient has no evidence of active TB. If presence of latent TB is established, then treatment must have been initiated and maintained according to local country guidelines prior to Day 1 (Baseline).
18. Chest X-ray, computerized tomography (CT) scan, or MRI with evidence of ongoing infectious or malignant process, obtained within 12 weeks prior to Baseline, and evaluated by a qualified physician.
19. Past medical history record of, or current infection with, human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus prior to Baseline.
20. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for skin Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed).

[redacted]

21. Current severe progressive or uncontrolled disease which in the judgment of the Investigator renders the patient unsuitable for the study or puts the patient at increased risk (eg, myocardial infarction within 26 weeks prior to Baseline).
22. Inability or unwillingness to undergo repeated venipuncture (eg, because of poor tolerability or lack of access to veins).
23. Any medical or psychiatric condition which, in the Investigator's opinion, would preclude the patient from adhering to the protocol or completing the study per protocol.
24. History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to Baseline.
25. Plans for administration of live vaccines during the study period or in the 6 weeks prior to Baseline.
26. Not willing to limit UV light exposure (eg, sunbathing and/or the use of tanning devices) during the course of the study.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Secukinumab for s.c. injection will be supplied in single boxes each containing 2 PFS of 150 mg secukinumab in a 1 mL liquid formulation.

Each 300 mg dose will be administered as 2 PFS injections of 150 mg secukinumab.

All study drugs will be labelled appropriately.

5.1.2 Additional study treatment

No additional treatment is requested for this study.

5.2 Treatment groups

For Treatment Period 1 (Baseline to Week 24) all patients will receive the same treatment:

- Secukinumab 300 mg s.c. will be self-administered at Baseline, weekly at Week 1, Week 2 and Week 3 and every 4 weeks thereafter (ie, Week 4, 8, 12, 16 and 20).

At Week 24, all patients will be assessed in term of PASI response and either randomized to one of the 4 treatment groups in Treatment Period 2 (Week 24 to Week 52) or withdrawn from the study.

Patients with at least a 90% reduction in PASI score from Baseline will be randomized at Week 24 on a 1:1 basis to Group 1 or Group 2:

- Group 1 (recommended maintenance treatment): secukinumab 300 mg s.c. every 4 weeks (Week 24, 28, 32, 36, 40, 44 and 48).
- Group 2 (experimental dosing maintenance treatment): secukinumab 300 mg s.c. every 6 weeks (Week 24, 30, 36, 42 and 48).

[redacted]

Patients with less than 90% reduction in PASI score from Baseline at Week 24 but achieved at least a 75% reduction in PASI score from Baseline are eligible for dose frequency intensification and will be randomized on a 1:1 basis to either Group 3 or Group 4:

- Group 3 (recommended maintenance treatment): secukinumab s.c. 300 mg every 4 weeks (Week 24, 28, 32, 36, 40, 44 and 48).
- Group 4 (experimental maintenance treatment): secukinumab s.c. 300 mg every 2 weeks (Week 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 48).

Patients with a reduction in PASI score from Baseline of less than 75% at Week 24 are not eligible for randomization and will be discontinued from the study.

5.3 Treatment assignment, randomization

At the Screening Visit, every patient will be registered in an Interactive Response Technology (IRT) system. The Investigator or his/her delegate will ensure that the patient fulfills all the inclusion/exclusion criteria. At Baseline, every patient will receive study medication kits assigned by the IRT system.

At the Randomization Visit (Week 24) all patients will be assessed in term of PASI response and eligible patients will be randomized by the IRT system to one of the 4 treatment groups in Treatment Period 2 (Week 24 to Week 52) or withdrawn from the study.

Patients with at least a 90% reduction in PASI score from Baseline will be randomized at Week 24 on a 1:1 basis to Group 1 or Group 2:

- Group 1 (recommended maintenance treatment): secukinumab 300 mg s.c. every 4 weeks (Week 24, 28, 32, 36, 40, 44 and 48).
- Group 2 (experimental dosing maintenance treatment): secukinumab 300 mg s.c. every 6 weeks (Week 24, 30, 36, 42 and 48).

Patients with less than 90% reduction in PASI score from Baseline at Week 24 but achieved at least a 75% reduction in PASI score from Baseline are eligible for dose frequency intensification and will be randomized on a 1:1 basis to either Group 3 or Group 4:

- Group 3 (recommended maintenance treatment): secukinumab s.c. 300 mg every 4 weeks (Week 24, 28, 32, 36, 40, 44 and 48).
- Group 4 (experimental maintenance treatment): secukinumab s.c. 300 mg every 2 weeks (Week 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 48).

Patients with a reduction in PASI score from Baseline of less than 75% at Week 24 are not eligible for randomization and will be discontinued from the study. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment group and study drug to be dispensed to the patient. The randomization number will not be communicated to the IRT user.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and Investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of Patient Numbers to randomization numbers. These randomization numbers are linked to the different treatment groups, which in turn are linked to medication numbers.

[redacted]

A separate medication list will be produced under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the study drug.

The randomization scheme for patients will be reviewed and approved by a qualified team member.

Further details will be described in the IRT manual.

5.3.1 IRT Stratification

Randomization will be stratified at the Week 24 visit (Randomization) by body weight. This stratification ensures balanced allocation of patients to treatment groups within the weight strata. The strata will be "body weight ≥ 90 kg" or "body weight < 90 kg." All treatment groups will be stratified by body weight assessed at Week 24. The randomization scheme for patients will be reviewed and approved by a randomization expert.

5.4 Treatment blinding

The study drug will be self-administered by the patient in an open-label fashion as described in Section 5.5. A blinded PASI assessor who has no access to the randomization details must perform all PASI and IGA mod 2011 efficacy assessments for Treatment Period 2 (Week 24 to Week 52). To reduce measurement variability, it is recommended that the same blinded PASI assessor performs all PASI and IGA mod 2011 assessments for a single patient.

The blinded PASI assessor must not participate in any study-related activities that could compromise the blinding and should solely concentrate on the skin examination for PASI and IGA mod 2011 assessments.

The blinded assessor will know at Week 24 if a patient will achieve the PASI 90 criterion or not. However, in the analysis phase of the study, PASI and IGA mod 2011 data for Group 1 will be compared only with corresponding data from Group 2 (both groups represent the patient pool meeting a PASI 90 response at Week 24). PASI and IGA mod 2011 data from Group 3 and Group 4 will be treated separately in the study analysis.

A PASI assessor should be qualified by education, training and experience (eg, a physician). Training for the blinded assessor will be offered at the Investigator Meeting and/or during study center initiation and/or at the latest before the blinded PASI assessor will do the first assessment. The training should be documented appropriately. If the blinded assessor observes a potential safety event (eg, an AE) during the assessments he/she must inform, without delay, the unblinded team that has all the available patient information. The unblinded team is responsible to further examine the transferred observation without delay. All observations need to be documented appropriately by the blinded assessor including the transfer of the information to the unblinded team. The unblinded team is responsible to subsequently report any potential safety event to the Novartis. See also Section 7.

The blinded PASI assessors will use electronic devices to document and report PASI and IGA mod 2011 data. Data will be collected in a central database separated from the main clinical database to mitigate risks for unblinding events and reduce cross-team interactions. The results of the PASI and IGA mod 2011 assessments will be sent electronically to Novartis or a designated Contract Research Organization (CRO). Details of the process are described in a user manual and will be part of the blinded assessor training.

[redacted]

All remaining assessments will be performed in an unblinded manner.

5.5 Treating the patient

5.5.1 Patient numbering

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

Upon signing the informed consent form (ICF), the patient is assigned the next available sequential number by the Investigator. At each study center, the first patient is assigned Patient Number 1, and subsequent patients are assigned consecutive numbers (eg, the second patient is assigned Patient Number 2, and the third patient is assigned Patient Number 3).

The Investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register the patient into the IRT. The study center should select the electronic Case Report Form (eCRF) book with a matching Patient Number from the electronic data capture (EDC) system to enter data. If the patient fails to be treated for any reason, the IRT should be notified that the patient was not treated.

At least the following information should be completed on the eCRFs for a patient who screen fails: demography, informed consent, inclusion/exclusion criteria, AEs (if applicable), SAEs (if applicable), death (if applicable), withdrawal of consent (if applicable) and patient screening details.

If a patient is rescreened for the study, the patient must sign a new ICF and will be issued a new Patient Number. The date of the new informed consent signature must be entered in the eCRF. Informed consent for a rescreened patient as for a newly screened patient must be obtained prior to performing any study related assessments or collecting any data for the Screening Visit. There is no limit on the number of times a patient can be rescreened. For rescreening all Screening assessments must be performed in accordance with the protocol (including QuantiFERON® TB-Gold In-Tube test), except for the chest X-Ray or TB work-up, if applicable, if performed within 12 weeks prior to Baseline.

5.5.2 Dispensing the investigational treatment

Each study center will be supplied by Novartis with study drug in packaging of identical appearance. The study drug packaging has a 2-part label. Investigator staff will select the study drug to dispense to the patient using the medication kit number as provided by the IRT system on the label of the study drug kit. Immediately before dispensing study drug 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 Patient Number.

After Week 24, once the home study drug administration applies, patients will be expected to perform home drug administrations at the protocol-specified timepoints. For these cases, the Investigator will dispense, supported by IRT, an appropriate number of investigational treatment packages for home administrations and detach the outer part of the label from the packaging as indicated above. The patients will record details including the date of administration at home and will return the used medication and packaging at their next visit to

the study center. Patients will be asked to return all unused medication and packaging at each scheduled study visit.

Study center staff will record in the appropriate documents the dates of the administration.

5.5.3 Handling of study drug

The study drug must be received by designated personnel at the study center, handled and stored safely and properly, and kept in a secured location to which only these designated personnel have access. Upon receipt, all study drugs should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization Quality Assurance.

The study drug must be stored in a refrigerator from 2 to 8°C (36 to 46°F) with restricted access to designated personnel, and must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations. The study drug should be protected from the light and must not be frozen.

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 drug but no information about the patient except for the medication number.

A pharmacist, Investigator or other qualified study center personnel must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability log that will be kept in a secured location to which no blinded site staff (ie, blinded assessor for PASI and IGA mod 2011) would have access to. Monitoring of drug accountability will be performed by a field monitor performing site visits and done at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused study drug, 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.

Patients will be asked to return all unused study drug and packaging at every study visit. A final reconciliation will be done by the site for the last study visit. Details for handling the home study drug administration will be provided separately.

[redacted]

5.5.4 Instructions for prescribing and taking study drug

Secukinumab will be self-administered by patients during the study after the study assessments (including completion of PROs) and scheduled blood samples have been performed.

For Treatment Period 1, all patients will be assigned to the same study drug regimen (300 mg secukinumab s.c. every week for the first 4 weeks, and thereafter every 4 weeks) and will self-administer the study drug at the study site under the supervision and guidance of site personnel at the time-points indicated in Table 5-1. To allow for comparable treatment group data on fixed study visits, patients will be trained for home drug administration prior to Treatment Period 2. If needed, a caregiver can be trained for home administration to provide support to the patient; corresponding training should be documented in the source data at the study center.

For Treatment Period 2, patients will be assigned to 4 different treatment interval groups depending on their PASI response at Week 24. Patients will self-administer their first dose of randomized study drug at Week 24 at the study site under the supervision and guidance of site personnel. Thereafter, patients will self-administer the study drug at either the study site or at home depending on the scheduled study drug administration by study group in Table 5-1 and Table 6-2.

Table 5-1 Timing of study drug administration by study group

	Treatment Period 1	
	(Self-administration at Study Site)	(Self-administration at Home)
All Patients		
All patients	Baseline and Weeks 1, 2, 3, 4, 8, 12, 16 and 20	None
	Treatment Period 2	
	(Self-administration at Study Site)	(Self-administration at Home)
Patients with PASI ≥ 90		
Group 1 (every 4 weeks)	Week 24, 28, 32, 36, 40, 44 and 48	None
Group 2 (every 6 weeks)	Week 24, 36, 48	Week 30, 42
Patients with 75 ≤ PASI < 90		
Group 3 (every 4 weeks)	Week 24, 28, 32, 36, 40, 44 and 48	None
Group 4 (every 2 weeks)	Week 24, 28, 32, 36, 40, 44 and 48	Week 26, 30, 34, 38, 42 and 46

Study drug will be dispensed and self-administered with the support of qualified personnel during office visits in accordance with local laws and regulations or self-administered at home. The blinded assessor for PASI and IGA mod 2011 must not be part of the study drug dispensing or administration process.

The first administration of secukinumab by qualified site personnel will occur at the Baseline visit (Visit 2) after all study scheduled assessments have been performed (and inclusion/exclusion criteria are confirmed) and directly after a blood sample for PK is

[redacted]

collected (pre-dose sample), if applicable. All study drug kits assigned to the patient during the study will be recorded in the IRT.

All dates of injections administered to the patient during the study must be recorded on appropriate eCRF pages for dosage administration.

All injections administered at the study center should be documented in the source documents for drug handling; patient's home administrations should also be documented.

The Investigator should promote compliance by instructing the patient to attend visits and perform home drug administration as planned so the study drug can be administered exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the Investigator if he/she is unable for any reason to attend a study visit as scheduled.

5.5.5 Permitted dose adjustments and interruptions of study drug

Treatment interruptions are not permitted. No dose adjustment of study drug is permitted and no interruption of the study drug should be planned during the study.

If a dose of secukinumab was dispensed by the IRT but not administered to a patient, this deviation event must be recorded in the eCRF.

5.5.6 Rescue medication

Use of rescue medication is not permitted during the study.

Patients who do not respond, ie non responders (defined by a PASI < 50 response), or achieve only partial response, ie partial responders (defined by a PASI < 75 response) to the study drug until Week 24 will be withdrawn from the study. This allows for different treatment options outside of the study.

Pooled data from Phase 3 studies shows that 87.6 % of biologic-naïve patients achieved at least the PASI 75 criterion at Week 24 and can therefore be regarded as treatment responders.

5.5.7 Concomitant treatment

All treatments administered during the 6 months prior to start of study drug (including any treatments started during the Screening period) for any reason NOT including psoriasis will be entered in the concomitant medications eCRF or the procedures and significant non-drug therapies eCRF. The start date, end date, dose, unit, frequency, route and reason for administration or change are to be recorded.

In addition, psoriasis treatments used from the time the patient started to treat psoriasis will be reported on the prior psoriasis therapy eCRF. All topical treatments, systemic treatments and phototherapies for psoriasis administered prior to Day 1 (Baseline Visit) will be entered in the prior psoriasis therapy eCRF page (Section 6.2.2).

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

[redacted]

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

Concomitant medications are allowed if not listed in Table 5-2. Dose adjustments of these medications should be avoided during the study. If a dose adjustment of these medications does occur, it must be recorded on the appropriate eCRF page.

Mild to moderate topical corticosteroids (TCS) will be allowed, only if:

- **medication was used for an indication other than psoriasis and <u>not</u> on the area <u>affected</u> with psoriasis.**
- medication was used for up to 7 consecutive calendar days which includes the first day or less.

Higher than moderate TCS are not allowed from the Week 24 visit (post-dose) to Week 52.

To determine the potency of a TCS regimen, the Investigator/qualified site staff should take into account the potency of the topical steroid, active ingredient, its concentration, base, place of administration, the condition of the patient's skin, and the frequency of administration.

Use of these TCS must be recorded in the eCRF.

There is no restriction on the use of anti-histamines or of corticosteroid drops in the eye or ear during the study.

5.5.7.2 Permitted concomitant medications for psoriasis

After the Screening period, the use of concomitant medication for psoriasis in all body regions is restricted to bland emollients (not supplied by Novartis) and other non-medicated interventions (not listed in Table 5-2). Use of bland emollients must be recorded on the concomitant medications eCRF. Use of any other non-medicated interventions must be recorded in the eCRF.

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

Once the patient is screened and if the patient has intolerable scaling and/or itching, the use of bland emollients is permitted. The use of bland emollients should be avoided during the 12 hours preceding a scheduled study visit.

A mild to moderate potency TCS will be allowed for the treatment of the face, scalp, and genitoanal area during the Screening period. These TCS must be stopped the day before Day 1 (Baseline Visit).

Use of these TCS will be recorded on the prior psoriasis therapy eCRF if TCS was used for psoriasis or under Concomitant medications eCRF if TCS was used for any other reason.

5.5.7.3 Permitted concomitant medications for psoriatic arthritis

The use of non-steroidal anti-inflammatory drugs (NSAIDs), analgesic treatments or any other treatment given to treat psoriatic arthritis will be permitted only if not listed in Table 5-2.

Use of these medications must be recorded on the appropriate eCRF page.

[redacted]

Dose adjustments of these medications should be avoided during the study. If a dose adjustment of these medications should occur, they must be recorded in the eCRF.

5.5.8 Prohibited Treatment

Use of any treatments displayed in Table 5-2 that could confound the efficacy of secukinumab will NOT be allowed during the study for any indication and washout periods for these treatments are indicated in Table 5-2. If the use of these treatments is required, then the patient must NOT be enrolled into the study. The Investigator/qualified site staff must instruct the patient to notify them about any new treatments he/she takes after the start of the study drug. All prohibited medications and significant non-drug therapies administered after the patient starts study drug must be recorded in the eCRF.

If a prohibited treatment listed in Table 5-2 was used during the study, the patient must discontinue use of the prohibited treatment if he/she wishes to continue in the study. At the discretion of the Investigator/qualified site staff, if the patient's use during the study of a prohibited treatment listed in Table 5-2 presents undue safety risk for the patient, the patient should be discontinued from study drug as per Section 5.5.10. If the patient received a live virus vaccination during the study, the patient must discontinue study drug and complete the end-of-study visit.

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

[redacted]

Table 5-2 Prohibited treatment

Prior Therapy (before Baseline Visit [Day 1])	
Prohibited treatments[†, ‡]	**Washout period (before Baseline Visit [Day 1])**
Ustekinumab, Guselkinumab	No prior use allowed
Secukinumab	No prior use allowed
Any biologic drug directly targeting IL-17 or the IL-17RA (other than secukinumab)	No prior use allowed
Alefacept, efalizumab	No prior use allowed
Biological immunomodulating agents other than above (eg, etanercept, adalimumab, infliximab)	No prior use allowed
Other new systemic treatments, eg apremilast	No prior use allowed
Any biologic drug against psoriasis or against any other indication	No prior use allowed
Other systemic immunomodulating treatments[§] (eg, methotrexate, cyclosporine A, corticosteroids (oral, i.v., intramuscular, s.c., intra-articular, transdermal)[§], cyclophosphamide)	4 weeks
Other systemic psoriasis treatments (eg, retinoid, fumarates)	4 weeks
Photo chemotherapy (eg, PUVA)	4 weeks
Phototherapy (eg, UVA, UVB)	2 weeks
Topical treatment that is likely to impact signs and symptoms of psoriasis (eg, vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids)	2 weeks
Live virus vaccinations	6 weeks
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Prohibited regimen of Topical Corticosteroids (TCS)	
TCS higher than moderate potency on any body location	2 weeks
TCS mild to moderate potency on any body location <u>other than</u> the face, scalp and/or genitoanal area	2 weeks
TCS mild to moderate potency <u>on</u> the face, scalp and/or genitoanal area	1 day*

[redacted]

Prior Therapy (before Baseline Visit)	Stable period (before Baseline Visit [Day 1])
Any other treatment known to worsen psoriasis (eg, beta-blockers, calcium channel blockers, lithium)	Stable at least 4 weeks before Baseline Visit (Day 1)
Concomitant therapy (after Baseline Visit [Day 1])	
Prohibited regimen of Topical Corticosteroids (TCS)	**Prohibited period**
TCS any potency	Baseline Visit (Day 1) to Week 24 visit (pre-dose)**
TCS any potency on area affected with psoriasis	Week 24 visit (post-dose) to Week 52 visit
TCS higher than moderate potency	Week 24 visit (post-dose) to Week 52 visit
TCS mild to moderate potency used for more than 7 consecutive days	Week 24 visit (post-dose) to Week 52 visit

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

‡ In case of undue safety risk for the patient, the patient should discontinue study drug at the discretion of the Investigator/qualified site staff. If the patient received a live virus vaccination during the study, the patient must discontinue study drug.

§ Inhalative CS with only a topical effect (eg, to treat asthma) are not considered "**systemic** immunomodulating treatments" and are therefore acceptable as comedication.

* Mild to moderate TCS used on the face, scalp and/or genitoanal area must be stopped at the latest on the day prior to the Baseline Visit (Day 1).

** No TCS is allowed during Treatment Period 1 (from Baseline Visit [Day 1] to Week 24 visit pre-dose).

5.5.9 Exposure to light

Patients 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.

5.5.10 Discontinuation of study drug

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

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

If discontinuation occurs for any reason in a treatment period, the Investigator/qualified site staff must make every effort to determine the primary reason for a patient's discontinuation from the study drug. This information will then be recorded in the eCRF.

Study drug *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 patient's overall status, prevent the patient from continuing study drug (for example, sepsis or serious infection).
- Any laboratory abnormalities that in the judgment of the Investigator/qualified site staff taking into consideration the patient's overall status, prevents the patient from continuing study drug.
- Pregnancy (see Section 6.5.6 and Section 7.4).

[redacted]

- Use of prohibited treatment as per recommendations in Section 5.5.8.

Patients discontinued from study drug will NOT be considered discontinued from the study. The Investigator/qualified site staff must record the date and primary reason for stopping the study drug.

At the time of the study drug discontinuation visit, IF it has been at least 4 weeks after the last dose of study drug, THEN the assessments described for the end of treatment period 1 (EOT1) visit/Week 24 (for early discontinuation during **Treatment Period 1**) or the end of treatment period 2 (EOT2) visit/Week 52 (for early discontinuation during **Treatment Period 2**) should be completed at this visit. The patient will then return per appropriate schedule for visit Week 60, if applicable.

IF it has not been at least 4 weeks after the last dose of study drug at the time of the study drug discontinuation visit, THEN the patient should be scheduled to return 4 weeks post last dose for their EOT1 visit (Week 24) or EOT2 visit (Week 52) assessments, respectively. The patient will then return per appropriate schedule for the Week 60 visit, if applicable.

The Investigator/qualified site staff must contact the IRT when the patient completes the EOT1 visit (Week 24) or EOT2 visit (Week 52) assessments to register the patient's early completion of the study due to study drug discontinuation. See Section 6 for the required assessments of these patients after study drug discontinuation.

5.5.11 Discontinuation from a treatment-free period

If discontinuation occurs for any reason in the treatment-free follow-up period, the Investigator/qualified site staff must make every effort to determine the primary reason for a patient's premature withdrawal from the study. This information will then be recorded by Investigator/qualified site staff on the applicable section of the eCRF.

See Section 6 for the required assessments of those patients who discontinue from the follow-up period.

5.5.12 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

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

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

5.5.13 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the Investigator should show "due diligence" by contacting the

[redacted]

patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, eg dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until his/her scheduled end of study visit would have occurred.

5.5.14 Emergency breaking of assigned treatment code

Not applicable.

5.5.15 Study completion and post-study drug

Study completion is defined as all patients who have been enrolled and completed the study as per 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.

If there is the possibility that patients can participate in an extension study the eligibility criteria and all study details should be explained in a corresponding study protocol.

5.5.16 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as a discontinued patient as described in Section 5.5.10. 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 (IRB/IEC) of the early termination of the study.

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. Patients should be seen for all visits on the designated day or as closely as possible to the original planned visit schedule (recommended visit windows are in Table 6-1). Every effort should be made to respect the timeframe for all visits.

If for any reason the patient is a screen failure, the patient may be rescreened. If the reason for screen failure is regarded as a transient constraint for study participation then there is no restriction on the number of times a potential patient may be rescreened or on how much time must pass from the date of screen failure and the date of rescreening.

IF a patient rescreens for the study, THEN the patient must sign a new ICF and be issued a new Patient Number prior to any Screening assessment being conducted for the patient under the new Screening Patient Number. For all patients, the Investigator/qualified site staff will record if the patient was rescreened on the eCRF and any applicable Screening numbers the patient was issued prior to the current Screening number.

The date of the new informed consent signature must be entered on the eCRF to correspond to the new Screening Patient Number. Informed consent for a rescreened patient 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 in accordance

with the protocol, except for the chest X-ray or TB work-up, if applicable, if performed not more than 12 weeks prior to Day 1 (Baseline). If patients do not have a chest X-ray available within 12 weeks of the projected Day 1 date, the X-ray should be performed after it is certain the patient meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation.

If the date of the TB work-up is less than 12 weeks from Baseline then the TB work-up does not have to be repeated; however, the patient must repeat the QFT performed by the central laboratory.

During the Treatment Periods 1 and 2, patients may be seen at an unscheduled visit, eg, if they experience deterioration of psoriasis or suspected AEs. During these unscheduled visits, study drug will NOT be administered.

Recommended visit windows

Treatment periods:

- ± 2 days for Baseline, Week 1, Week 2, Week 3 and Week 4 and for Week 24.
- ± 2 days for all study drug home administrations.
- ± 5 days for all other study visits.
- Visit 1 and Visit 2 must not be conducted at the same day and all relevant information for Visit 2 must be available before treating the patient. The screening period might not be longer than 4 weeks.

For patients who discontinue study drug prematurely before the end of the Treatment Period 1 for any reason other than withdrawal of informed consent, the Week 24 (planned EOT1) visit must be performed at least 28 days (4 weeks) after the last drug administration and the patient should then enter the treatment free follow-up period, if applicable.

For patients who discontinue study drug prematurely before the end of the Treatment Period 2 for any reason other than withdrawal of informed consent, the Week 52 (planned EOT2) visit must be performed at least 28 days (4 weeks) after the last drug administration and the patient should then enter the treatment free follow-up period, if applicable.

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

For Group 3 and Group 4 at a minimum, patients will be contacted for safety evaluations during the 12 weeks following the last dose of study drug, including final contact at the 12-week point or the 30 days point following the last study visit (whichever is later). Documentation of attempts to contact the patient should be recorded in the patient's record.

Recommended order of assessments:

The recommended order of PRO assessment for completion by the patient is as follows:

- DLQI
- Patient's assessment of pain, itching and scaling

[redacted]

- EQ-5D© Health Status Questionnaire
- WPAI-PSO

The recommended order of efficacy and other assessments, which will be completed by the Investigator/qualified site staff, is as follows:

- IGA mod 2011 assessments (performed by the blinded assessor)
- PASI assessments (performed by the blinded assessor)
- Review PRO data (at applicable visits).
- Physical examination (at applicable visits).
- All remaining study visit procedures (eg vital signs measurements) are to be completed prior to study drug dosing
- Safety blood samples and PK blood sample will be collected
- Contact IRT to register the patient visit and enter all data as applicable.
- Self-administration of study medication. Note: if needed, a caregiver of the patient can be trained for home administration to provide support to the patient; corresponding training should be documented in the source data at the study center (see Section 5.5.4).

Table 6-1 Assessment schedule

Period	Scr	Treatment Period 1										Treatment Period 2							FU	Unscheduled Visit[d]	Comments
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19		
Week	-4 to BL[e]	BL	1	2	3	4	8	12	16	20	24 a, b	28	32	36	40	44	48	52 c	60		
Recommended visit window (days)			±2	±2	±2	±2	±5	±5	±5	±5	±2	±5	±5	±5	±5	±5	±5	±5	±5		
Informed consent	X																				
Demographics	X																				
Inclusion/exclusion criteria	X	X																			These assessments are supported by and stored within the source documentation. Data relating to inclusion/exclusion criteria are captured in the corresponding eCRF.
Smoking history	X																				
Psoriasis: medical history / previous psoriasis therapies	X																				
Other medical history and prior medications	X																				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
Height	X																			X	
Weight	X	X									X							X	X	X	
Vital signs	X	X				X		X	X		X	X		X			X	X	X	X	
Laboratory sampling: safety panel (Clinical chemistry including urine, hematology)	X	X				X		X	X		X	X		X			X	X	X	X	For processing of samples please refer to the manual of the central lab.

[redacted]

Period	**Scr**	**Treatment Period 1**										**Treatment Period 2**							**FU**	**Unscheduled Visit[d]**	**Comments**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**		
Week	**-4 to BL [e]**	**BL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24 a, b**	**28**	**32**	**36**	**40**	**44**	**48**	**52 c**	**60**		
Recommended visit window (days)			±2	±2	±2	±2	±5	±5	±5	±5	**±2**	±5	±5	±5	±5	±5	±5	±5	±5		
Chest X-ray (or CT/MRI)	S																			S	Where a patient has not had a chest X-ray, chest CT or chest MRI, CT performed within 3 months prior to Screening, an image should be obtained once it is clear that the patient meets the other inclusion/exclusion criteria in order to minimize unnecessary exposure X-ray radiation.
QuantiFERON® TB-Gold In-tube test[e]	X																			X	see lab manual
Serum pregnancy test	X																			X	Only for females of child-bearing potential.
Urine pregnancy test (local)		X				X		X	X		X			X				X	X	X	In the event of a positive urine pregnancy test, study drug must be withheld and a serum pregnancy test performed at the same visit. A urine pregnancy test is not required for a woman who is sterile or who is post-menopausal.
ECG (standard 12-lead)		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	
BSA	X	X																X		X	

[redacted]

Period	**Scr**	**Treatment Period 1**										**Treatment Period 2**							**FU**	**Unscheduled Visit[d]**	**Comments**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**		
Week	**-4 to BL [e]**	**BL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24 a, b**	**28**	**32**	**36**	**40**	**44**	**48**	**52 c**	**60**		
Recommended visit window (days)			±2	±2	±2	±2	±5	±5	±5	±5	**±2**	±5	±5	±5	±5	±5	±5	±5	±5		
IGA mod 2011	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
DLQI		X				X		X			X			X			X	X		X	
WPAI-PSO		X				X		X			X			X			X	X		X	
Assessment of pain, itching and scaling		X				X		X			X			X			X	X		X	
EQ-5D©		X				X		X			X			X			X	X		X	
AE assessment (including injection site reactions)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of rebound																			X		Unscheduled rebound assessment only to be done at an unscheduled visit that occurs during the post-treatment follow-up period.
Randomization by IRT											X										
IRT contact such as for registration or drug supply including home administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
PK blood sample		X						X			X			X			X			X	Samples will be shipped by the sites and stored by the central laboratory. Samples will be shipped to reference laboratories for analysis. Samples need to be taken before dosing.

[redacted]

Period	**Scr**	**Treatment Period 1**										**Treatment Period 2**							**FU**	**Unscheduled Visit[d]**	**Comments**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**		
Week	**-4 to BL [e]**	**BL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24 a, b**	**28**	**32**	**36**	**40**	**44**	**48**	**52 c**	**60**		
Recommended visit window (days)			±2	±2	±2	±2	±5	±5	±5	±5	**±2**	±5	±5	±5	±5	±5	±5	±5	±5		
Check self-administration log												S	S	S	S	S	S	S		S	Patients must return the self-administration log along with all dispensed PFS and drug packaging at every visit, if applicable.
Complete Screening period eCRF	X																				
Complete end of Treatment Period 1 eCRF											X										
Complete end of Treatment Period 2 eCRF																		X			

Footnotes:
a Visit 11, patients will have the last assessment for Treatment Period 1 performed prior to administration of study drug.
b Visit 11 assessments must be completed for patients who discontinue study drug prematurely during Treatment Period 1; patient should then enter the post treatment follow-up period, if applicable.
c Visit 18 assessments must be completed for patients who discontinue treatment prematurely during Treatment Period 2.
d Unscheduled visit – assessments at discretion of the Investigator.
e A repeat QuantiFERON® TB-Gold In-Tube test is recommended if the result of the first QuantiFERON® TB-Gold In-Tube test is “indeterminate”. The patient must be referred for a follow-up TB work-up (as per local guidelines) if either the first or the repeat test is “positive” or if the results of both tests are “indeterminate”. If the first test is indeterminate, the Investigator may decide not to repeat the test and to proceed directly to the work-up, though this is not recommended. The patient will not be eligible for enrollment if “active TB is present “or if “latent TB is present” and is untreated as per local guidelines.

[redacted]

Abbreviations:
AE: adverse event; BL: baseline; CT: computer tomography; DLQI: Dermatology Life Quality Index; ECG: electrocardiogram; eCRF: electronic case report form; EOT: end of treatment; EQ-5D©: EuroQOL 5-Dimension Health Questionnaire; FU: follow-up; IGA: Investigator's Global Assessment; IRT: interactive response technology; MRI: magnetic resonance imaging; PASI: Psoriasis Area and Severity Index; PFS: pre-filled syringe; PK: pharmacokinetic; S = assessment to be recorded on source documentation Scr: screening; TB: tuberculosis; Uns: unscheduled visit; WPAI-PSO: Work Productivity and Activity Impairment Questionnaire-Psoriasis; X = assessment to be recorded on clinical database

Table 6-2 Overview of study drug administration for Treatment Period 2

Visit	**11**		**12**		**13**		**14**		**15**		**16**		**17**	**18**
Week	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**52**
Recommended visit window (days)	±2	±2	±5	±2	±5	±2	±5	±2	±5	±2	±5	±2	±5	±5
Study drug administration														
Group 1	**S**		**S**		**S**		**S**		**S**		**S**		**S**	
Group 2	**S**			**H**			**S**			**H**			**S**	
Group 3	**S**		**S**		**S**		**S**		**S**		**S**		**S**	
Group 4	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	

Abbreviations: H = home administration; S = administration at study center

[redacted]

6.1 Information to be collected on screening failures

All patients who have signed informed consent but discontinue prior to first intake of study drug on Day 1 (Baseline Visit) are considered to be screen failures. If a patient discontinues prior to or at Day 1, the reason for screen failure will be entered on the Screening Phase Disposition eCRF.

The Screening Visit date, the Demography eCRF, the Informed Consent eCRF, the Inclusion/Exclusion eCRF, and the Patient Rescreening eCRF must be completed. The AE eCRF should be completed for any AEs that occurred during the Screening period. The withdrawal of consent eCRF must be completed if consent was withdrawn during the Screening period. The Death eCRF should be completed in the case of a death during the Screening period.

For all patients who sign the informed consent and enter into the next period of the study, all AEs occurring after the informed consent is signed will be recorded on the AE eCRF.

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

If a patient discontinues the study prior to entering the randomized, assessment-blinded treatment period (Treatment Period 2), the IRT should be notified and the reason for not being randomized (at Week 24) will be entered in the eCRF. The patient should be seen as soon as possible and treated as a discontinued patient as described in Section 5.5.10.

6.2 Patient demographics/other baseline characteristics

All Baseline assessments should be performed prior to first study drug administration. Please refer to Table 6-1.

6.2.1 Demographics

Patient demographic and Baseline characteristic data will be collected at the Screening Visit. Data to be collected on all patients include: date of birth (if allowed by local data privacy rules), age, sex, race, as well as height and weight.

6.2.2 Psoriasis medical history / previous psoriasis therapies

Disease history will be collected at the Screening Visit. The information to be collected and entered as Psoriasis History and Prior Psoriasis Therapies includes the following:

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

[redacted]

6.2.3 Smoking history

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

6.2.4 Co-morbidities – cardiovascular medical history

Any information pertaining to cardiovascular medical history assessed prior to signing of informed consent should be reported as cardiovascular history. Cardiovascular risk factors will also be recorded.

6.2.5 Relevant medical history / current medical conditions

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

Patients with Crohn's Disease are eligible for the study, but should be followed closely.

Significant findings that are observed after the patient has signed the ICF and that meet the definition of an AE must be recorded in the AE summary pages.

6.2.5.1 Chest X-Ray

A chest X-ray, CT scan, or MRI obtained within 12 weeks prior to enrollment will be used to determine eligibility. If patients do not have a chest X-ray, CT scan, MRI available within 12 weeks prior to enrollment, a chest X-ray (or chest MRI at pre-specified sites) only must be done after it is fairly certain the patient meets the other inclusion/exclusion criteria in order to minimize unnecessary exposure to X-ray radiation for patients.

If the chest X-ray, CT scan, or MRI evaluated by a qualified physician shows evidence of ongoing infection or malignancy and the patient was not treated subsequent to the X-ray (CT scan or MRI), the patient will not be eligible to enter the study.

6.2.6 Prior and concomitant medications

Concomitant medications and prior medications taken over the 6 months preceding the study Screening Visit (Visit 1) will be captured in the eCRF and any other relevant medication taken before 6 months at the discretion of the Investigator.

6.2.7 Determination of tuberculosis status

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

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

[redacted]

6.2.7.1 QuantiFERON TB-Gold In-Tube assay

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

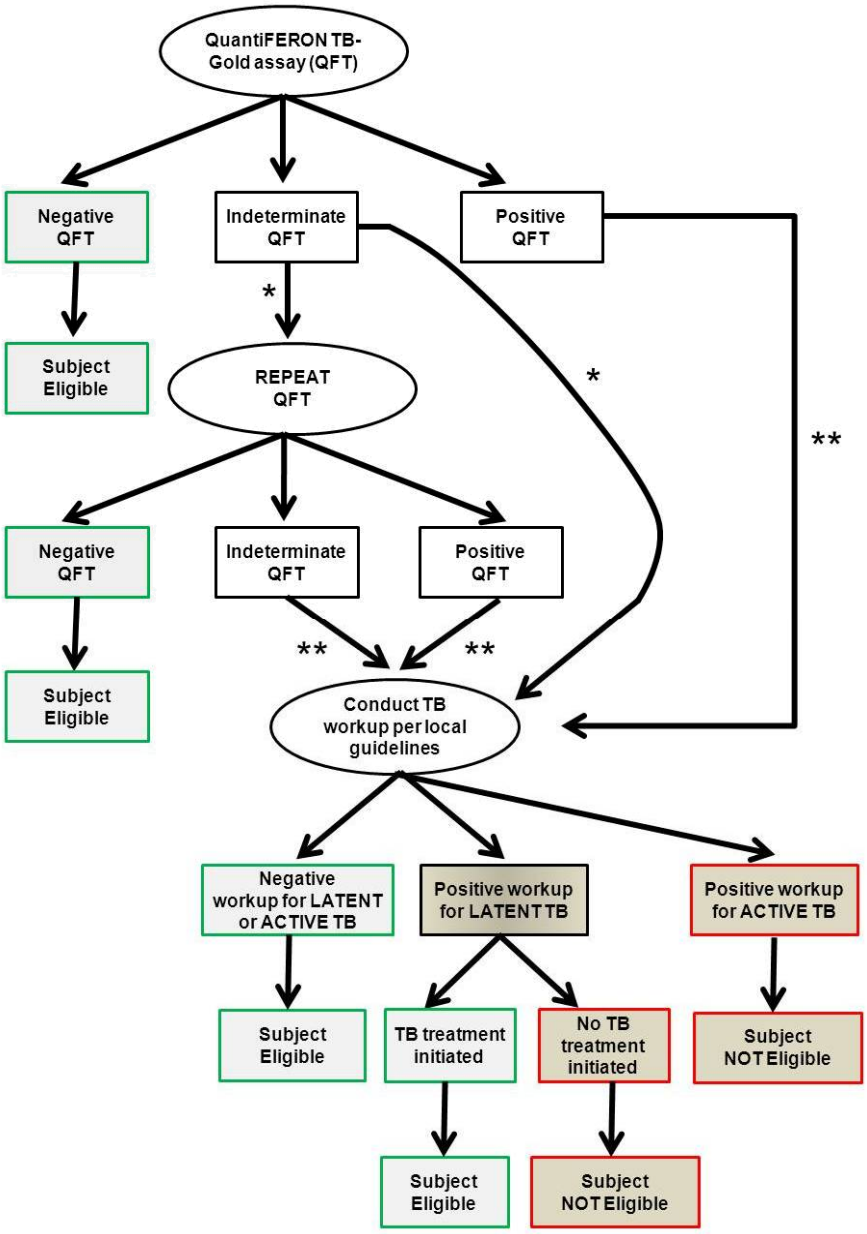
- If the test result is negative, the patient may be enrolled.
- If the test result is positive, the Investigator should perform work-up for the test result as per local procedures. If a TB work-up was conducted prior to the Screening of the patient, results of the work-up can be used to assess eligibility if the work-up was conducted within 12 weeks prior to Baseline:
    - Patients who are **positive** for latent TB per work-up may be enrolled in the study if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration. Patients **positive** for active TB per work-up are not eligible for the study.
    - Patients who are **negative** for TB (no signs of latent or active TB) per work-up may be enrolled in the study.
- If the test result is **indeterminate**, it is **recommended to repeat the test once**. The Investigator may decide to skip the repetition of the test and proceed directly to the work-up (this is however not recommended). If a TB work-up was conducted prior to Screening the patient, results of the work-up can be used to assess eligibility if the work-up was conducted within 12 weeks prior to Day 1 (Baseline Visit).
    - If the second test is **negative**, the patient may be enrolled.
    - If the second test is **positive or** indeterminate, the Investigator should perform work-up as per local guidelines. The patient will not be eligible for enrollment if:
        - "active TB is present" or
        - "latent TB is present" and is untreated as per local guidelines.

      Patients negative for TB per work-up (no signs of latent or active TB) may be enrolled into the study if the work-up was conducted within 12 weeks prior to Day 1 (Baseline Visit).
- If eligibility is being assessed with only one test result and a TB work-up (ie, no second TB test will be performed), the TB test to assess eligibility must have been done via the central laboratory for the study within the Screening period (within 4 weeks prior to Day 1 [Baseline Visit]) and TB work-up will only be considered if it was completed within 12 weeks prior to Baseline. Patients who are positive for latent TB per work-up may be enrolled to the study if sufficient treatment has been initiated according to local routine

[redacted]

clinical practice and will be maintained for the prescribed duration. Patients positive for active TB per work-up are not eligible for the study. Patients negative for TB per work-up (no signs of latent or active TB) may be enrolled to the study.

Figure 6-1 Tuberculosis screening flowchart



Abbreviations: TB: tuberculosis, QFT: QuantiFERON® TB-Gold In-Tube test

The patient will not be eligible for enrollment if "active TB is present" or if "latent TB is present and is untreated as per local guidelines."

* If the first QuantiFERON® TB-Gold In-Tube test is indeterminate, the Investigator may choose to perform a second test or refer the patient for TB work-up per local guidelines.

** If the result of any QuantiFERON® TB-Gold In-Tube test is "positive" or the results of 2 sequential tests are "indeterminate," the patient must be referred to have a TB work-up per local guidelines (if no work-up within 12 weeks prior to enrollment is available).

[redacted]

6.2.8 Other baseline characteristics

Baseline characteristic data to be collected for all patients include (all laboratory tests are performed centrally except where indicated; see also Table 6-1) the following:

- 12-lead ECG, vital signs, hematology, clinical chemistry, physical examination, height, weight, past medical history record of HIV, Hepatitis B or C status, DLQI©, WPAI-PSO, Patient's assessment of pain, itching and scaling, EQ-5D©, as well as assessments of PASI, BSA and IGA mod 2011 and PK, if applicable. A serum pregnancy test will be performed for women of child-bearing potential.

6.3 Treatment exposure and compliance

All doses of study drug administered will be recorded on the appropriate Dosage Administration Record eCRF page. Patient compliance to the study drug should be assessed by qualified site personnel at each study visit using the study kits and documentation regarding study drug dispensation and administration.

Compliance will also be assessed continuously during the conduct of the study by Novartis study personnel using medication kits and corresponding documentation. Study drug doses and corresponding dates of self-administration at home should be documented in a self-administration log. Patients are required to return the self-administration log as well as all dispensed study medication at every visit back to the investigational site for a compliance check.

6.4 Efficacy

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

Efficacy assessments

The efficacy assessments are recommended to be completed in the following order by the blinded PASI assessor. In all cases, the assessor will be blind to treatment allocation. Please refer to Section 5.4.

- IGA mod 2011
- PASI

All remaining study visit procedures (eg laboratory sample collection, vital signs measurements, PK sample, if applicable) are recommended to be completed prior to administration of study drug.

Patient-reported outcomes

Patient reported outcomes are recommended to be performed in the following order, prior to any Investigator assessments:

- DLQI©
- Patient's assessment of pain, itching and scaling
- EQ-5D©
- WPAI-PSO

[redacted]

6.4.1 Investigator's Global Assessment Modified 2011

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

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

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

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

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

Table 6-3 Investigator global assessment modified 2011 rating scale

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

Note: Involvement of nails is not part of the assessment

6.4.2 Assessment of total body surface area and psoriasis area and severity index

The blinded PASI assessor will complete the PASI assessment as indicated in Table 6-1. Whenever possible, the same blinded PASI assessor should perform this assessment at all visits.

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for full details of the PASI assessment). The following calculations will be done: Each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added up to estimate the total BSA affected by chronic plaque psoriasis.

The PASI scoring system is further described in Table 6-4.

[redacted]

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

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

Because the head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the BSA, 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 6-4 .

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

The Baseline value for analysis of the PASI is collected at Day 1 (Baseline Visit).

Patients require a total BSA affected by plaque-type psoriasis of ≥ 10% and a PASI score of ≥ 10% at Baseline to be eligible for this study.

[redacted]

Table 6-4 Psoriasis area and severity index 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% 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

[redacted]

6.4.3 Definitions of efficacy variables based on psoriasis area and severity index

The following definitions will be used in this study based on the Committee for Medicinal Products for Human Use (CHMP) guidelines for psoriasis (CHMP/EWP/2454/02 corr):

- **PASI 50 response (partial response):** patients achieving ≥ 50% improvement (reduction) in PASI score compared to Baseline are defined as PASI 50 responders.
- **PASI 75 response**: patients achieving ≥ 75% improvement (reduction) in PASI score compared to Baseline are defined as PASI 75 responders.
- **PASI 90 response**: patients achieving ≥ 90% improvement (reduction) in PASI score compared to Baseline are defined as PASI 90 responders.
- **PASI 100 response / remission**: complete clearing of psoriasis (PASI = 0).

6.4.3.1 Definitions of relapse and rebound

For plaque psoriasis, in addition to the assessment of PASI, the Investigator will assess whether new pustular psoriasis, new erythrodermic psoriasis, or more inflammatory psoriasis has occurred (yes/no).

- **Relapse**: when the achieved maximal PASI improvement from Baseline is reduced by >50% (CHMP/EWP/2454/02 corr).
- **Rebound:** A patient will be considered to have experienced a rebound, if PASI increases to ≥125% of Baseline PASI, or if new pustular psoriasis, new erythrodermic psoriasis, or more inflammatory psoriasis occurs within 8 weeks after the last dose of study drug has been received (CHMP/EWP/2454/02 corr).

6.4.4 Appropriateness of efficacy assessments

PASI scores outcome measures, the assessment of the severity of the psoriasis symptoms and the extent to which the patient's body area is affected by the disease, is mandated by the EMA for the clinical investigation of medicinal products for the treatment of psoriasis (CHMP/EWP/2454/02 corr).

As indicated in Section 6.4.1, the IGA mod 2011 scale has been developed by Novartis (Langley et al 2013) in collaboration with health authorities, in particular the FDA and has been used extensively in the secukinumab in psoriasis Phase 3 program.

6.5 Safety

From Day 1 (Baseline Visit), all blood draws and safety assessments must be performed prior to study drug administration. Appropriate safety assessments (eg, evaluation of AEs and SAEs) should be repeated after the dose of study drug is administered.

- Evaluation of all AEs and SAEs including injection site hypersensitivity reactions, vital signs, laboratory assessments and occurrence of infections (see Section 7)
- Physical examination
- Vital signs
- Height and weight

[redacted]

- Laboratory evaluations (hematology, clinical chemistry including urine samples)
- 12-Lead ECGs
- Pregnancy and assessments of fertility

6.5.1 Physical examination

A physical examination, including general appearance, will be performed as indicated in Table 6-1.

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

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

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the patient signing informed consent must be included in the Medical History screen on the patient's eCRF. Significant findings made after the signing of the informed consent which meet the definition of an AE must be recorded on the AE screen of the patient's eCRF (Section 7.1).

6.5.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed as indicated in Table 6-1. After the patient has been sitting for 5 minutes, with back supported and both feet placed on the floor, systolic and diastolic **blood pressure will be measured twice** (measurements separated by 1 to 2 minutes) using a validated device with an appropriately sized cuff and each BP measurement will be recorded in the source (Mancia et al 2007). In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. If possible, assessments should be performed by the same study site staff member throughout the study.

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

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

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

[redacted]

6.5.3 Height and weight

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

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

If possible, body weight assessments should be performed by the same study site staff member and using the same scale throughout the study.

6.5.4 Laboratory evaluations

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

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

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

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

For clinically notable thresholds please refer to Appendix 1 or the lab manual.

6.5.4.1 Hematology

Hematology assessments will include hemoglobin, hematocrit, red blood cell (RBC) count, WBC count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count. Hematology assessments will be measured at scheduled study visits, within the visit window, as specified in Table 6-1.

6.5.4.2 Clinical chemistry

Serum chemistry will include urea, creatinine, total bilirubin, alanine aminotransferase (ALT)/serum glutamic pyruvate transaminase (SGPT), aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), gamma glutamyl transferase (GGT), alkaline phosphatase, sodium, potassium. Serum chemistry will be measured at scheduled study visits, within the visit window, as specified in Table 6-1.

For a local analysis of urine, dipsticks will be provided by the central laboratory to the sites for the assessment. Sites should record the results in the source documentation and report these in the eCRF for each patient, as specified in Table 6-1.

6.5.5 Electrocardiogram

A standard 12-lead ECG will be performed as indicated in the schedule of assessments (Table 6-1). The Investigator/qualified site staff must review and initial the tracing. The tracing must then be stored with the patient's source documents.

If the ECG findings are clinically relevant and would prevent the patient from participating in the study (taking into account the patient's overall status as well as the medication profile), the

[redacted]

patient should be recorded as a screen failure, should NOT be enrolled and should not receive treatment.

All ECGs will be independently reviewed by a central reader. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG Investigator manual. Although there is no exclusion criterion specifically based on the ECG, the Baseline ECG performed at the Baseline Visit must be reviewed for major abnormalities before dosing at the Baseline Visit.

6.5.6 Pregnancy and assessments of fertility

A serum β-hCG test will be performed in all pre-menopausal women as shown in Table 6-1.

All pre-menopausal women who are not sterile at Screening will also have a urine pregnancy test performed locally as indicated in Table 6-1.

Any woman with a confirmed positive pregnancy test during Screening is not eligible for enrollment.

A positive urine pregnancy test during the treatment periods of the study requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, study drug must be definitively discontinued, as described in Section 5.5.10.

6.5.7 Appropriateness of safety measurements

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

6.6 Other assessments

- Health-related quality of life (HRQoL) assessments as shown in Table 6-1.

6.6.1 Resource utilization

Not applicable.

6.6.2 Health-related Quality of Life

The impact of psoriasis on various aspects of patient's HRQoL will be assessed by the following validated instruments, each of which will be performed as indicated in Table 6-1:

- DLQI©
- Patient's Assessment of pain, itching and scaling
- EQ-5D©
- Work Productivity and Activity Impairment Questionnaire Psoriasis (WPAI-PSO)

All these quality of life assessments should be completed by the patient before the patient sees the study physician (Investigator or designee) who will perform the Investigator assessments.

All these quality of life assessments will be completed in the language the respondent is most familiar with, at the scheduled visit before the patient sees the Investigator for clinical assessments. The patient should be given sufficient space and time to complete the

[redacted]

questionnaires. The study coordinator should check the questionnaires for completeness and encourage the patient to complete any missing responses. Prior to clinical examination, the Investigator should review the completed questionnaires for responses that may indicate potential AEs or SAEs. If AEs or SAEs are confirmed, the Investigator must record the events as per instructions given in Section 7 of the protocol.

Investigators should not encourage patients to change the responses reported in the completed questionnaires.

6.6.2.1 Dermatology Life Quality Index

The DLQI© is a 10-item general dermatology disability index designed to assess HRQoL in adult patients with skin diseases such as eczema, psoriasis, acne, and viral warts (Finlay and Khan 1994; Basra et al 2008).

The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 33 different skin conditions and is available in 85 languages. The DLQI© is the most frequently used instrument in randomized controlled studies in dermatology.

The recall period is the previous week, and the instrument takes 1 to 2 minutes to complete.

Each item has 4 response categories ranging from 0 (not at all) to 3 (very much). "Not relevant" is also a valid response and is scored as 0. The DLQI© total score is a sum of the 10 questions. Scores range from 0 to 30, with higher scores indicating greater HRQoL impairment. Each subscale of the DLQI© may also be analyzed separately.

6.6.2.2 Patient's Assessment of pain, itching and scaling

A self-administered, 11-point numeric rating scale (NRS, 0-10) will be used to evaluate the patient's assessment of their current pain, itching and scaling. Respondents will answer the following questions for the assessment of:

Pain: Overall, how severe was your psoriasis-related pain over the past 24 hours?

Itching: Overall, how severe was your psoriasis-related itch over the past 24 hours?

Scaling: Overall, how severe was your psoriasis-related scaling over the past 24 hours?

Patients have to rate their pain, itching, and scaling from 0 to 10 (11-point scale), with the understanding that the 0 represents the absence or null end of the pain, itching, or scale intensity (ie, no pain, itching or scaling) and the 10 represents the other extreme of pain, itching, or scaling intensity (ie, pain, itching or scaling as bad as it could be). The number that the patient selects represents his or her intensity score.

6.6.2.3 EuroQOL 5-Dimension Health Status Questionnaire

The EQ-5D© is a generic instrument developed by the EuroQoL group to assess patients' health status for clinical and economic appraisal, which was introduced in 1990 (The EuroQol Group 1990). Available in over 100 official language versions, it provides a simple descriptive profile and a single index value for health status. The recall period is "today", and

[redacted]

the instrument takes 1 to 2 minutes to complete. The instrument essentially consists of 2 pages – the EQ-5D© descriptive system and the EQ visual analogue scale. The EQ-5D© descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response levels: no problems, slight problems, moderate problems, severe problems and unable. The patient is asked to indicate the patient's health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions.

A unique health state is defined by combining one level from each of the 5 dimensions. Health states may be converted into a single number, called weighted index, by applying values (also called weights) to each of the levels in each dimension (Dolan et al 1997). The weighted index constitutes a measure of utility. The VAS records the respondent's self-rated health on a vertical 20-cm VAS where the endpoints are labeled "best imaginable health state" and "worst imaginable health state." This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

6.6.2.4 Work Productivity and Activity Impairment Questionnaire Psoriasis

The WPAI-PSO version 2 is a self-administered questionnaire derived from the WPAI-General Health (Reilly et al 1993), which comprises 6 questions regarding the effects of psoriasis on the patient's ability to work and to perform regular activities and is based on their experiences in the previous 7 days. The questionnaire quantifies the number of hours that the respondent was unable to work and, using a 10-point scale, evaluates the extent to which the respondent's psoriasis affected their productivity while working. For respondents who are not in paid employment, the questionnaire evaluates the extent to which the individual respondent's psoriasis affects their ability to perform regular daily activities.

6.6.3 Pharmacokinetics

At selected study sites, blood samples will be collected for PK at the scheduled visits as indicated in Table 6-1. All blood samples will be taken by direct venipuncture. Blood samples (approximately 2 mL, not less than 1.5 mL) will be collected into serum separating tubes. The blood sample will be allowed to clot for a minimum of 30 minutes at room temperature prior to harvesting of the serum. The serum will be obtained by centrifugation at approximately 2500 rpm for 10 minutes. Serum samples will be placed on ice, split into 2 aliquots (polypropylene tubes) and then stored (within 30 minutes of serum collection by centrifugation) at -70°C to -20°C (approximately) prior to shipment to the central laboratory. Shipment of stored aliquots from the site to the central lab should be on a pre-specified basis. To the extent possible, the site should send each aliquot to the central laboratory separately. The central lab will ship one aliquot of the samples on dry ice to the analytical laboratory. The remaining aliquots must be kept at the central laboratory as a backup sample. Remaining samples will only be disposed of after approval by the Clinical Trial Team (typically 6 to 12 months after the Clinical Study Report (CSR) is published).

The actual sample collection date and reference time point of collection will be entered in the eCRF, as appropriate. Sampling problems will be noted in the eCRF as well.

[redacted]

For a detailed description of the complete PK blood sampling refer to the corresponding laboratory manual.

6.6.3.1 PK sample handling, labeling and shipment instructions

A laboratory manual will be provided with detailed information on sample collection, sample handling and shipment. Tubes and labels will be provided by the central laboratory with study/sample type and sample number preprinted on the label.

6.6.3.2 Pharmacokinetic sample stability

Secukinumab is stable in serum samples for up to 12 months at or below -15°C and for up to 32 months at or below -70°C.

6.6.3.3 Pharmacokinetic analytical methods

An ELISA method will be used for bioanalytical analysis of secukinumab in serum with an anticipated lower limit of quantification (LLOQ) of 80 ng/mL. A detailed description of the methods used to assess AIN457 concentration will be provided in the bioanalytical raw data for the study and the respective Bioanalytical Data Report.

6.6.4 Other biomarkers

If there is the possibility that patients can participate in a biomarker sub-study then eligibility criteria and all study details should be explained in a corresponding separate study protocol.

7 Safety monitoring

7.1 Adverse events

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

All patients who have signed informed consent and are entered into the next period of the study will have all AEs **occurring after informed consent is signed** recorded on the AE eCRF.

The occurrence of AEs should 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, laboratory test, or other assessments.

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

[redacted]

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

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

Adverse events should be recorded in the AE eCRF with the following information:

- Severity grade:
  - Mild: usually transient in nature and generally not interfering with normal activities.
  - Moderate: sufficiently discomforting to interfere with normal activities.
  - Severe: prevents normal activities.
- Relationship of the AE to the study drug(s) (Suspected: Yes or No)
- Duration (start and end dates, or if the event is ongoing at the final examination).
- Whether it constitutes a SAE (see Section 7.2.1).
- Action taken with the study treatment.
- Concomitant medication or therapies taken.
- Outcome.

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (ie, further observation only); study drug temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the AE should be recorded on the AE eCRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should 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.

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

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

[redacted]

7.2 Serious adverse events

7.2.1 Definition of SAE

A Serious Adverse Event (SAE) is defined as event which:

- Is fatal or life-threatening.
- Results in persistent or significant disability/incapacity.
- Constitutes a congenital anomaly/birth defect.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for*:*
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Is medically significant, ie, defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events. All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.2.

7.2.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit, or 12 weeks after the last study drug (if applicable), must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 day-period should only be reported to Novartis if the Investigator suspects a causal relationship to study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the Investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow-up information) is collected and recorded in English on the paper SAE Report Form or the electronic SAE Form within the data capture

[redacted]

system (where available). The Investigator must assess the relationship to each specific component of the study drug (if the study drug consists of several components).

SAEs (initial and follow-up) that are recorded *electronically* in the eCRF system (if this function is available) should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety and Epidemiology immediately after Investigator signature or 24 hours after entry, whichever occurs first.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study drug 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 drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

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

Liver events are divided into 2 categories:

- Liver events of special interest which consist of elevated transaminases and/or alkaline phosphatase and/or total bilirubin (elevated liver function tests [LFTs])
- Medically significant liver events which are considered as SAEs and which consist of marked elevations of LFTs and / or pre-specified AEs

Please refer to Table 14-1 in Appendix 2 for complete definitions of liver events.

Any liver event which meets the criteria for "**medically significant**" event as outlined in Table 14-1 of Appendix 2 should follow the **standard procedures for SAE reporting** as described in Section 7.2.

Every liver event as defined in Table 14-1 of Appendix 2 should be followed up by the Investigator/qualified site staff as summarized below. Detailed information is outlined for liver laboratory trigger in Table 14-2 in Appendix 2.

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate

[redacted]

- A causality assessment of the liver event via exclusion of alternative causes (eg, disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution

These investigations can include serology tests, imaging and pathology assessments, and hepatologist's consultancy, based on Investigator/qualified site staff's discretion.

All follow-up information, and the procedures performed, should be recorded on appropriate eCRF pages.

7.4 Pregnancy reporting

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the Investigator/qualified site staff to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug.

Any SAE experienced during pregnancy must be reported on the SAE Report 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 eCRFs with the Investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries in the eCRFs, the adherence to the protocol and to Good Clinical Practice (GCP), the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for as appropriate. Key study personnel must be available to support the field monitor during these visits.

In addition, monitoring of treatment accountability will be performed continuously by a field monitor during site visits and at the completion of the study. The field monitor will regularly check that study drug is being stored, prepared, dispensed and accounted as appropriate and ensure that only unblinded personnel would have access to.

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, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The Investigator must also keep the original ICF signed by the patient (a signed copy is given to the patient).

[redacted]

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables.

Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated unblinded Investigator staff will enter the data required by the protocol into the eCRF system. Designated Investigator study center staff will not be given access to the system until they have been trained.

The blinded assessor for the PASI and IGA mod 2011 assessment will report data in a separate database. The blinded assessor must not have access to details that could compromise the blinding.

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 study center staff. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the Investigator will receive copies of the patient data for archiving at the investigational study center.

8.3 Database management and quality control

Novartis staff or designated CRO staff review the data entered into the eCRFs by Investigator/qualified study center staff for completeness and accuracy and instruct the Investigator/qualified study center staff to make any required corrections or additions. Queries are sent to the investigational study center using an electronic data query. Investigator/qualified study center 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 study center. Investigator/qualified study center staff 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 study center.

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

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO). All ECGs will be independently reviewed by a central reader. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG Investigator manual.

The blinded assessors for PASI and IGA mod 2011 assessments will use electronic devices to report PASI and IGA mod 2011 data. These data will be collected centrally and the results

[redacted]

will be sent electronically to Novartis (or a designated CRO). In case electronic devices cannot be used a paper-based process is acceptable and details of the whole process are described in a separate user manual.

Randomization codes, data about all study drug dispensed to the patient and some efficacy data will be tracked using IRT. The system will be supplied by Novartis staff or a vendor that will also manage the database. The database will be sent electronically to Novartis (or a designated CRO). Details are provided in a user manual.

8.4 Data Monitoring Committee

In alignment with the EMA Guideline on Data Monitoring Committees (DMCs) (EMEA/CHMP/EWP/5872/03 Corr) no DMC is deemed to be required for this Phase 3b clinical study. A pharmacovigilance review concluded that substantial amount of safety data for the study drugs have been collected through all study phases and that a DMC would not be beneficial for the study. Furthermore, the study population is not considered to have an elevated risk of more severe outcomes during this study, which is also in accordance with US, Department of Health and Human Services FDA guidelines (Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006).

8.5 Adjudication Committee

Not applicable.

9 Data analysis

For the analysis of Treatment Period 1 (until/including Week 24) all patients will receive the same treatment:

- secukinumab 300 mg s.c. every 4 weeks

For the analysis of Treatment Period 2 (maintenance period Week 24 to Week 52) the following treatment groups are utilized.

Only patients with at least a 90% reduction in PASI score from Baseline will be randomized at Week 24 on a 1:1 basis to either Group 1 or Group 2:

- Group 1 (recommended maintenance treatment): secukinumab 300 mg s.c. every 4 weeks.
- Group 2 (experimental maintenance treatment): secukinumab 300 mg s.c. every 6 weeks.

Patients who did not achieve a PASI 90 at Week 24 but achieved at least a PASI 75 response are eligible for dose frequency intensification and will be randomized to either Group 3 or Group 4:

- Group 3 (recommended maintenance treatment): secukinumab s.c. 300 mg every 4 weeks.
- Group 4 (experimental maintenance treatment): secukinumab s.c. 300 mg every 2 weeks.

Patients with less than a 75% reduction in PASI score from Baseline at Week 24 are not eligible for randomization and will be discontinued from the study.

[redacted]

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, median, 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 CIs will be displayed.

9.1 Analysis sets

The **Safety Set for Treatment Period 1 (SAF-TP1)** will include all patients who received at least one dose of study drug during this treatment period.

The **Safety Set for Maintenance Treatment Period 2 (SAF-TP2)** will include all patients who were randomized and received at least one dose of study drug at- or after the Week 24 visit. For safety evaluations, the patient groups of PASI 90 responders and PASI 75 responders who do not achieve a PASI 90 response will be pooled; therefore, only 3 dosing groups will be compared:

- secukinumab 300 mg s.c. every 2 weeks (patients from Group 4)
- secukinumab 300 mg s.c. every 4 weeks (patients from Group 1 pooled with Group 3)
- secukinumab 300 mg s.c. every 6 weeks (patients from Group 2)

Patients will be analyzed according to the treatment they received.

The **Full Analysis Set for Treatment Period 2 of PASI 90 Responders (FAS-P90R)** will include all patients who are rated as PASI 90 responders at the Week 24 visit, were randomized to treatment groups 1 or 2 and who received at least one dose of study drug at- or after visit Week 24.

The **Full Analysis Set for Treatment Period 2 of PASI 75 Responders who do not achieve a PASI 90 Response (FAS-P75P)** will include all patients who are rated as PASI 75 responders who do not achieve a PASI 90 response at visit Week 24, were randomized to treatment Group 3 or 4 and who received at least one dose of study drug at- or after visit Week 24.

The **Per-Protocol Set for Treatment Period 2 of PASI 90 Responders (PP-P90R)** will include all patients from the FAS-P90R who complete the study as scheduled without any major deviations from the protocol which may affect the primary outcome of this study. Such deviation will be defined in the Data Validation Plan or similar document and in the protocol of the blind data review without knowledge of the treatment group assignment.

Efficacy evaluations will be performed according to the treatment assigned at randomization.

9.2 Patient demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and Baseline characteristics. The number and percentage of patients in each category will be presented for categorical variables. Separate tables will be produced for all patients treated (SAF-TP1, totals only) and

[redacted]

for patients randomized into the maintenance period (FAS-P90R and FAS-P75P, each by treatment group).

9.2.1 Medical history

Any condition entered as medical history or current medical conditions at Baseline (including cardiovascular risk factors) will be coded using the MedDRA dictionary. They will be summarized by MedDRA system organ class (SOC) and preferred term of the MedDRA. Summaries for psoriasis specific medical history will also be provided.

9.3 Treatments

The duration of exposure to study drug will be summarized for all patients treated (SAF-TP1, totals only) and for patients randomized into the maintenance period (FAS-P90R and FAS-P75P, each by treatment group). Compliance will be calculated in percent as the number of injections administered divided by the number of injections scheduled according to the protocol.

9.3.1 Prior and concomitant treatment

Prior and concomitant medications will be summarized by treatment group in separate tables.

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

Medications will be presented in alphabetical order, by anatomical therapeutic classification (ATC) codes and grouped by anatomical main group. Tables will also show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

In addition, significant prior and concomitant non-drug therapies and procedures will be summarized by primary SOC and MedDRA preferred term.

9.4 Analysis of the primary variable

9.4.1 Variable

The primary variable is the maintenance of the PASI 90 response rate at Week 52 in the FAS-P90R, which is the proportion of patients who maintain their PASI 90 response assessed at Week 24 also at Week 52. The aim of the primary analysis of this study will be to demonstrate the non-inferiority of the 6-weekly dosing group compared to the 4-weekly dosing group with respect to the primary endpoint in the FAS-P90R.

9.4.2 Statistical model, hypothesis, and method of analysis

The statistical null-hypothesis to be rejected is that the odds ratio of maintaining a PASI 90 response for patients 4-weekly dosing versus patients on 6-weekly dosing exceeds the non-inferiority margin of $1+\delta$.

[redacted]

Let π_j denote the probability of a PASI 90 response at Week 52 for treatment group *j*, *j*=0, 1 where

- 0 corresponds to 4-weekly dosing
- 1 corresponds to 6-weekly dosing

The following hypothesis will be tested

$H_{0.1}$: $(\pi_0 /[1- \pi_0])/ (\pi_1 /[1- \pi_1]) \geq 1+\delta$ versus H_{A1}: $(\pi_0 /[1- \pi_0])/ (\pi_1 /[1- \pi_1]) < 1+\delta$

The **primary analysis** will be performed comparing dosing groups (Group 1 vs Group 2) with respect to the primary efficacy variable in a logistic regression model with the factors treatment, country, body weight (< 90 kg or ≥ 90 kg), and PASI 90 response (Y/N) at Week 16. The odds ratio with its corresponding 95% CI will be given (please notice that the upper limit of a 2-sided 95% CI is identical to the upper limit of a one-sided 97.5% CI, which would correspond to a one-sided test with significance level 2.5%). Additionally, a (one-sided) p-value for the shifted null-hypothesis will be computed.

9.4.3 Choice of the non-inferiority margin

Non-inferiority is defined as a difference in PASI 90 maintenance rate between 4- and 6-weekly dosing not exceeding 15% on a rate difference scale. Data from a pooled CAIN457A database (CAIN4572302 and CAIN4572303) suggest that the PASI 90 maintenance rate at Week 52 under 4-weekly dosing might be 81.8%. However, since the logistic regression model used for the primary analysis provides estimates on the odds-ratio scale, the numbers above have to be translated into this scale. Inserting these numbers into the respective formulas results in a non-inferiority-margin on the odds-ratio-scale of $1+\delta = 2.23$. Non-inferiority of 6-weekly vs 4-weekly dosing will be claimed, if the upper limit of the CI for the odds ratio does not exceed 2.23.

9.4.4 Handling of missing values/censoring/discontinuations

Patients who drop out prematurely and/or do not have a valid PASI assessment at Week 52 will be counted as non-responders. Patients with major protocol violations, but with a valid PASI assessment will be included in the ITT-analysis with their observed response.

The same algorithm will be used for the key secondary endpoint, the PASI 90 response in the FAS-P75P set. Missing values for other endpoints will not be replaced.

9.4.5 Supportive analyses

The primary analysis will be repeated for the Per-Protocol Set (PP-P90R). The impact of missing values will be explored using multiple imputation as a sensitivity analysis. The raw (unadjusted) response rates and their difference will be computed with the corresponding CI (option RISKDIFF in SAS PROC FREQ).

[redacted]

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The key secondary variable is the PASI 90 response rate at Week 52 in the FAS-P75P, ie, the proportion of patients with a PASI 75 response but also less than a PASI 90 response at Week 24 who achieve a PASI 90 response at Week 52. The key secondary analysis of this study will be to demonstrate superiority of the shortened 2-weekly dosing group compared to the 4-weekly dosing group in the FAS-P75P.

The statistical null-hypothesis to be rejected are that the odds ratio of gaining a PASI 90 response for patients on 2-weekly dosing versus patients on 4-weekly dosing = 1

Let π_j denote the probability of a PASI 90 response at Week 52 for treatment group j, $j = 0, 1$ where

- 0 corresponds to 2-weekly dosing
- 1 corresponds to 4-weekly dosing

The following hypothesis will be tested

$$H_{0.2}: (\pi_0 /[1- \pi_0])/ (\pi_1 /[1- \pi_1]) = 1 \text{ versus } H_{A2}: (\pi_0 /[1- \pi_0])/ (\pi_1 /[1- \pi_1]) \neq 1$$

This analysis will be performed comparing dosing groups (Group 3 vs Group 4) with respect to the key secondary variable in a logistic regression model with the factors treatment, country and PASI response (75% to 82% or 83% to 89%) at Week 24. The odds ratio with its corresponding 95% CI and p-value will be presented.

The key secondary analysis will be included in a confirmatory testing strategy. The key secondary hypothesis will be *a priori* ordered below the primary hypothesis. This means that no multiplicity adjustment of the significance level is required; however, confirmatory evidence will be claimed only if non-inferiority with regard to the primary endpoint has been successfully demonstrated before. Otherwise, the result for the secondary endpoint will be interpreted as being purely explorative, independent of the nominal p-value.

The time course of PASI response (absolute points and percentage change from Baseline) will be graphically displayed for treatment Group 1 to 4 as well as for the total Treatment Period 1 set. All other secondary variables (IGA mod 2011, QoL) will be analyzed descriptively using means and SDs for continuous and absolute and relative frequencies for categorical variables.

Appropriate statistical tests for group comparisons of these variables will be defined in the SAP.

9.5.2 Safety variables

For safety-evaluations, the patient groups of PASI 90 responders and those who achieve PASI 75 but not PASI 90 will be pooled for Group 1 and Group 3; therefore, only 3 dosing groups will be compared:

- secukinumab 300 mg s.c. every 2 weeks (patients from Group 4).
- secukinumab 300 mg s.c. every 4 weeks (patients from Group 1 pooled with Group 3).

[redacted]

- secukinumab 300 mg s.c. every 6 weeks (patients from Group 2).

Patients will be analyzed according to the treatment they received.

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

AEs will be summarized by presenting, for each treatment group, the number and percentage of patients

- having any AE,
- having an AE in each primary SOC and
- having each individual AE (preferred term).

Summaries will also be presented for AEs by severity and for study drug related AEs. If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary SOC, the patient will be counted only once with the greatest severity at the SOC level, where applicable.

These summaries will be presented separately for study periods (Treatment Period 1, Treatment Period 2, Post-Treatment Follow-up Period), and for complete treatment periods (Treatment Periods 1 and 2 and Follow-up). Separate summaries will be provided for deaths, SAEs, other significant AEs leading to discontinuation and AEs leading to study drug discontinuation.

9.5.3 Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation which might be carried out and reported as a separate activity.

9.5.4 Pharmacokinetics

Exploratory analysis to investigate the correlation between the PK data and efficacy outcomes will be performed. An indirect response model, driven by study drug concentration, will be used to characterize the time course of PASI response. Further details of the modeling approach will be specified in a modeling plan.

9.5.5 Pharmacogenetics/pharmacogenomics

Not applicable.

9.5.6 Biomarkers

Not applicable.

9.6 Interim analyses

No interim analysis is planned for this study.

[redacted]

9.7 Sample size calculation

Based on the pooled data from the CAIN457A program (CAIN4572302 and CAIN4572303), the PASI 90 response rate for biologics-naïve patients treated with secukinumab 300 mg s.c. was 74.3% at 24 weeks. Of those who were PASI 90 responders at Week 24, 81.8% of patients maintained their PASI 90 response until Week 52.

It is assumed that a dosing frequency of 6 weeks (Group 2) will differ in PASI 90 response up to 7% worse compared a dosing frequency of 4 weeks (Group 1). This assumption of a difference of maximally 7% is based on simulation of the PK levels obtained with maintenance treatments of secukinumab 300 mg every 6 weeks and the correlation between plasma levels and the clinical response seen in the secukinumab Phase 3 studies.

A total of 554 patients per group are required to achieve 90% power on a one-sided, 2.5% significance level to demonstrate the non-inferiority of 6-weekly vs 4-weekly dosing, if the true maintenance rates are 81.8% under 4-weekly and 74.8% under 6-weekly dosing and the non-inferiority margin is predefined as -15%.

The response rates underlying this estimation were obtained from pooled data of studies analyzed according to the ITT-principle using the same algorithm to handle drop-outs or protocol violations as in this present study. Therefore, the effect of drop-outs or protocol violations should be already accounted for in the effect estimates and no further adjustments of the sample size are required. However, to account for the fact that there might be minor differences (eg with respect to drop-out rates) between the historical data and the data to be observed in this study, the sample size will be rounded up slightly to 570 patients/group who should be randomized to Group 1 or Group 2 (giving a total of 1140 patients in both groups) of this study.

Assuming a PASI 90 response rate of 74% at Week 24, 1580 patients should be enrolled at Baseline in this study in order to achieve the required sample size for randomization at Week 24. This number still allows for some drop-out patients or patients withdrawing consent at or after randomization even after experiencing a PASI 90 response.

9.7.1 Power for the key secondary objective

As per the sample size calculation for the primary objective, 1580 patients will be enrolled into Phase 1 of the study. In the secukinumab database (CAIN457A2302 and CAIN457A2303) 13.3% of patients were in the category of PASI 75 but did not achieve PASI 90 at Week 24. In the present study, this would translate into 210 patients fulfilling the criteria to be randomized into the partial responder part of the maintenance phase.

Prior Phase 3results (CAIN457A2302 and CAIN457A2303) suggest that the PASI responses reach a maximum at around 16 to 24 weeks with a sustained effect until Week 52. The PASI 90 responder rate at Week 52 of patients treated with secukinumab 300 mg s.c. every 4 weeks who have a PASI 75 but no PASI 90 response at Week 24 is estimated to be 3.8%. This rate may be increased by 14% (to then 18%) by increasing the dosing frequency to 2-weekly after Week 24.

A sample size of 210 patients (105 per group) will provide more than 90% power on a two-sided, 95% significance level to detect differences in response rates for secukinumab

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intensified 2-weekly dosing compared to every 4 weeks, if the responder rates in these groups are about 4% vs. 18% at Week 52.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

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

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

Women of child bearing potential should be informed that taking the study drug 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 should not be entered in the study.

10.3 Responsibilities of the Investigator and IRB/IEC

Before initiating a study, the Investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the study protocol, written ICF, consent form updates, patient recruitment procedures (eg, advertisements) and any other written information to be provided to patients. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to

Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the study center is requested by a regulatory authority, the Investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

11 Protocol adherence

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

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. **Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval.** 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, Novartis should be notified of this action and the IRB/IEC at the study center should be informed within 10 working days or less, if required by local regulations.

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13 Appendix 1: Clinically notable laboratory values and vital signs

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

No specific action is pre-defined within this protocol to respond to specific abnormal laboratory values except for the follow-up requirement for liver events as specified in Appendix 2, as it will be decided by the investigator/qualified study center staff whether and which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the patient.

Liver Function and Related Variables (see also Appendix 2)

ALT (SGPT):	> 3 x Upper Limit of Normal (ULN)
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/L decrease from Baseline
Platelet count:	< Lower Limit of Normal (LLN)
White blood cell count:	< 0.8 x LLN
Neutrophils:	< 0.9 x LLN
Eosinophils:	> 1.1 x ULN
Lymphocytes:	> 1.1 x ULN

Urinalysis Variable

Protein urine dipstick:	++* (* ++ is ≥ 100 mg/dL)

[redacted]

14 Appendix 2: Liver event and laboratory trigger definitions and follow-up requirements

Table 14-1 Liver event definitions

	Definition/ threshold
Liver event of special interest	
Laboratory values	ALT (SGPT) or AST (SGOT) > 3 x ULN
	ALP > 2 x ULN
	TBL > 1.5 x ULN
Medically significant liver event (SAE)	
Laboratory values	ALT or AST > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	ALP > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	TBL > 3 x ULN
	Potential Hy's Law cases (defined as ALT/AST > 3 x ULN and TBL > 2 x ULN [mainly conjugated fraction] without notable increase in ALP to > 2 x ULN)
Adverse events	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 x ULN accompanied by general malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any event that links to a preferred term (PT) in the MedDRA dictionary falling under the SMQ sub-module "Drug-related hepatic disorders – severe events only"* or any "Hy's law case" PT

* These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

ALT = alanine aminotransferase, ALP = alkaline phosphatase, AST = aspartate aminotransferase, SMQ = standard medical query, TBL = total bilirubin, UNL= upper normal limit

[redacted]

Table 14-2 Liver event follow-up requirements

Criteria	Event type	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Medically significant	Discontinue the study drug immediately Hospitalize, if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST			
> 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists for *more than 2 weeks*, discontinue the study drug Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 x ULN accompanied by symptoms[b]	Medically significant	Discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator and Novartis Repeat LFT once or twice in the week If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 3 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
ALP (isolated)			
> 5 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, report to Novartis as an SAE Establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
> 2 to ≤5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator and Novartis Repeat LFT once or twice in the week If elevation persists,	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

[redacted]

Criteria	Event type	Actions required	Follow-up monitoring
		establish causality	
≤ 2 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
TBL (isolated)			
> 3 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (eg, reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 3 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Novartis Repeat LFT once or twice in the week. If elevation persists, establish causality	investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 1.5 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
Preferred terms			
Jaundice	Medically significant	Discontinue the study drug immediately Hospitalize the patient Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and GGT until resolution[c] (frequency at investigator discretion)
"Drug-related hepatic disorders - severe events only" SMQ AE	Medically significant	Discontinue the study drug hospitalization if clinically appropriate Report to Novartis as an SAE Establish causality	Investigator discretion

[a] Elevated ALT/AST > 3 x ULN and TBL > 2 x ULN but with no notable increase in ALP to > 2 x ULN

[b] General malaise, fatigue, abdominal pain, nausea, or vomiting, rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: return to Baseline values, stable values at 3 subsequent monitoring visits at least 2 weeks apart, remain at elevated level after a maximum of 6 months, liver transplantation, and death.

Alb = albumin, AESI = adverse event of special interest, ALP = alkaline phosphatase, GGT = gamma glutamyl transferase, LFT = liver function test, PT = prothrombin time, SMQ = standard medical query, TBL = total bilirubin, UNL= upper normal limit

[redacted]