NOVARTIS

Global Clinical Development - General Medicine

Secukinumab (AIN457)

Clinical Trial Protocol [CAIN457A2323] / NCT02748863

A multicenter, randomized, double-blind, placebo-controlled, 52-weeks study to demonstrate the efficacy, safety and tolerability of subcutaneous secukinumAb injections with 2 mL pre-fiLLed syringes (300 mg) in adUlt subjects with moderate to seveRE plaque psoriasis – ALLURE

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List of abbreviations

AE	Adverse Event
ALT/AST	Alanine Aminotransferase/Aspartate Aminotransferase
BDR	Bioanalytical Data Report
BSA	Body Surface Area
CFR	US Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
ClinRO	Clinician Reported Outcomes
COAs	Clinical Outcome Assessments
CPO	Country Pharma Organization
CRO	Contract Research Organization
CRP (hs-CRP)	Human C-reactive protein
CS	Corticosteroids
CSR	Clinical Study Report
CTCG	Common Toxicity Grade Criteria
DAR	Dose Administration Record
DLQI	Dermatology Life Quality Index
[redacted]	[redacted]
DS&E	Drug Safety & Epidemiology
EDC	Electronic Data Capture
ECG	Electrocardiogram
ECL	Electrochemiluminescence
eCRF	Electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma–glutamyl transferase
[redacted]	[redacted]
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
HRQOL	Health-related quality of life
HIV	Human Immunodeficiency virus
H	Home administrations
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identifier
IFU	Instructions For use

[redacted]	[redacted]
IGA mod 2011	Investigator's Global Assessment modified 2011
IL	Interleukin
i.m.	Intramuscular
IN	Investigator Notification
ITT	Intention-To-Treat-Analysis
i.v.	Intravenous
IRB/IEC	Institutional Review Board/Independent Ethics Committee
LDL	Low Density Lipoprotein
LLOQ	Lower Limit of Quantification
NIH	National Institutes of Health
IRT	Interactive Response Technology
NR/R	Non-responders, responders
MedDRA	Medical dictionary for regulatory activities
PASI	Psoriasis Area and Severity Index
PFS	Pre-filled syringe
PK	Pharmacokinetics
PPD	Purified protein derivative
PRO	Patient Reported Outcome (paper or electronic)
PsA	Psoriatic Arthritis
PUVA	Photochemotherapy (e.g. psoralen + UVA treatment)
QFT	QuantiFERON TB-Gold test
RPM	Revolutions Per Minutes
SAE	Serious Adverse Event
s.c.	Subcutaneous
SIAQ	Self-Injection Assessment Questionnaire
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamopyruvate Transferase
SST	Serum Separator Tubes
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TCS	Topical corticosteroid
TD	Study Treatment Discontinuation
Th17	T helper 17 cells
TNFα	Tumor necrosis factor alpha
ULN	Upper Limit of Normal
UV	Ultraviolet
UVA	Ultraviolet A, long wave 400 nm to 315 nm
UVB	Ultraviolet B, medium wave 315 nm to 280 nm
WBC	White blood cells/leukocytes
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: Screening/Recruitment, Wash-out, Treatment, and Follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CAIN457A2323
Title	A multicenter, randomized, double-blind, placebo-controlled, 52-weeks study to demonstrate the efficacy, safety and tolerability of subcutaneous secukinumAb injections with 2 mL pre-fiLLed syringes (300 mg) in adUlt subjects with moderate to seveRE plaque psoriasis - ALLURE
Brief title	Study of efficacy and safety of secukinumab 2 mL pre-filled syringe (300 mg) in subjects with moderate to severe plaque psoriasis
Sponsor and Clinical Phase	Novartis/Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The primary purpose of this study is to assess efficacy, safety and tolerability of 2 mL pre-filled syringe of 300 mg secukinumab. Results of this study will support the registration of secukinumab 300 mg in 2 mL pre-filled syringes. This 52-weeks, double-blind, randomized, parallel-group, and placebo-controlled study is using the recommended dose of 300 mg secukinumab which has been approved in Japan, USA, EU, Switzerland and other countries for the treatment of moderate to severe psoriasis in adults.
Primary Objective	The primary objective is to demonstrate the efficacy of secukinumab 300 mg when administered as 2 mL pre-filled syringes in subjects with plaque-type psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoint) at Week 12, compared to placebo.
Secondary Objectives	**Key Secondary Objectives** • To demonstrate the efficacy of secukinumab 300 mg when administered as 2 mL pre-filled syringes in subjects with plaque-type psoriasis with respect to PASI 90 and PASI 100 at Week 12, compared to placebo. • To demonstrate the efficacy of secukinumab 300 mg when administered as two 1 mL pre-filled syringes in subjects with plaque-type psoriasis with respect to PASI 100 at Week 12, compared to placebo. **Other Secondary Objectives** • To assess the efficacy of secukinumab 300 mg 2 mL pre-filled syringes on moderate to severe plaque-type psoriasis with respect to PASI score, IGA mod 2011 score, PASI 50 / 75 / 90 / 100 and IGA mod 2011 0 or 1 response up to Week 12 compared to placebo, and over time up to Week 52. • To investigate the clinical safety and tolerability of secukinumab 300 mg 2 mL pre-filled syringes as assessed by vital signs, clinical laboratory variables, and adverse events (AEs) monitoring, compared to placebo.

	• To assess the subject usability (ability to follow instructions for use and potential use-related hazards) and satisfaction with the secukinumab 2 mL pre-filled syringes utilizing a self-administered Self-Injection Assessment Questionnaire (SIAQ) and investigator / site staff observation of secukinumab 300 mg 2 mL pre-filled syringe administration. • To assess the effects of secukinumab 300 mg 2 mL pre-filled syringes with respect to Dermatology Life Quality Index (DLQI) 0 or 1 achievement and DLQI changes at Week 12 compared to placebo, and over time up to Week 52.
Study design	This is a 52-weeks multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in approximately 210 subjects with moderate to severe plaque-type psoriasis. The study consists of 4 epochs: Screening (of at least 1 week and up to 4 weeks), Treatment Epoch I (of 12 weeks), Treatment Epoch II (of 40 weeks) and Follow-up. The treatment-free phase of 8-weeks should only be completed in case subjects discontinue early. Subjects will be randomized using a 1:1:1 ratio to the following groups: secukinumab 300 mg regimen group (2 mL), secukinumab 300 mg regimen group (1 mL) or to placebo. After administration of the Week 12 dose, all subjects in the placebo group will continue the treatment based on their PASI 90 response status at Week 12. PASI 90 non-responders will receive in a 1:1 ratio either secukinumab 300 mg (2 mL) or secukinumab 300 mg (1 mL). PASI 90 responders will continue to receive placebo. All treatment groups have additional matching placebos.
Population	Approximately 210 subjects with moderate to severe plaque psoriasis will be randomized in approximately 57 centers worldwide. Approximately 250 subjects are expected to be screened to provide the number of randomized subjects. It is also expected to randomize approximately 20% of subjects who also suffer from psoriatic arthritis.
Key Inclusion criteria	Subjects eligible for inclusion in this study must fulfill all of the following criteria: 1. Subjects must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study related activity is performed. Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations. 2. Men or women of at least 18 years of age at the time of Screening. 3. Chronic plaque-type psoriasis present for at least 6 months and diagnosed before Randomization. 4. Moderate to severe psoriasis as defined at Randomization by: • PASI score of 12 or greater, **and** • IGA mod 2011 score of 3 or greater (based on a scale of 0 – 4), **and**

	• Body Surface Area (BSA) affected by plaque-type psoriasis of 10% or greater. 5. Candidate for systemic therapy. This is defined as a subject having moderate to severe chronic plaque-type psoriasis that is inadequately controlled by • Topical treatment and/or • Phototherapy and/or • Previous systemic therapy
Key Exclusion criteria	1. Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis) at Screening or Randomization. 2. Ongoing use of prohibited treatments. Washout periods detailed in the protocol have to be adhered to. Subjects not willing to limit UV light exposure (e.g., sunbathing and/or the use of tanning devices) during the course of the study will be considered not eligible for this study since UV light exposure is prohibited. Note: administration of live vaccines 6 weeks prior to Randomization or during the study period is also prohibited. 3. Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor. 4. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations. 5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. 6. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed). 7. History of hypersensitivity to any of study drug constituent.
Study treatment	Novartis will supply the following study drugs with the same liquid formulation: Investigational Treatment: • Secukinumab 300 mg, provided in a 2 mL pre-filled syringe Control Treatment: • Secukinumab 300 mg, provided as two injections of 1 mL pre-filled syringe (each 1 mL syringe containing 150 mg secukinumab) • Secukinumab matching placebo, provided in a 1 mL or 2 mL pre-filled syringe
Efficacy assessments	• Investigator's Global Assessment (IGA mod 2011; scale from 0 – 4)

	• Psoriasis Area and Severity Index (PASI; score from 0 – 72)
Key safety assessments	• Evaluation of all AEs and SAEs • Physical examination • Vital signs • Height and weight • Laboratory evaluations (hematology, clinical chemistry) • [redacted] • Pregnancy
Other assessments	• Usability and hazard assessment • SIAQ • DLQI • [redacted] • Pharmacokinetic parameter
Data analysis	The hypotheses will be tested sequentially and are included in a hierarchical testing strategy. Type-I-errors are set to keep a family-wise type-I-error of 2.5% (one-sided): • H_1: secukinumab 300 mg (2 mL s.c. injection) is not superior to placebo with respect to PASI 75 response at Week 12 • H_2: secukinumab 300 mg (2 mL s.c. injection) is not superior to placebo with respect to IGA mod 2011 0 or 1 response at Week 12 • H_3: secukinumab 300 mg (2 mL s.c. injection) is not superior to placebo with respect to PASI 90 response at Week 12 • H_4: secukinumab 300 mg (2 mL s.c. injection) is not superior to placebo with respect to PASI 100 response at Week 12 • H_5: secukinumab 300 mg (two 1 mL s.c. injections of 150 mg secukinumab) is not superior to placebo with respect to PASI 100 response at Week 12 The testing sequence will continue to H_3 at α (one-sided) only if both H_1 and H_2 have been rejected at α (one-sided). Similarly, the testing sequence will continue to H_4 at α (one-sided) only if H_3 testing has been rejected. In case, H_4 has been rejected at α (one-sided), the corresponding alpha (α) will be passed to the next hypothesis corresponding to H_5.
Key words	psoriasis, PASI, IGA mod 2011, secukinumab, pre-filled syringes

1 Introduction

1.1 Background

Psoriasis is a chronic relapsing disease of the skin characterized by variable clinical features. The lesions are classified as erythemato-squamous, which indicates that both the vasculature (erythema) and the epidermis (increased scale formation) are involved (Christophers et al 2003, Griffiths et al 2007).

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

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

Extensive clinical experience with TNFα-inhibitors has been collected over the past 10 years and these agents are generally considered to be effective and relatively safe (Papp et al 2005). However, a substantial percentage of patients do not respond well to treatment with a TNFα-inhibitor. This inadequate response may imply either a primary unsatisfactory response (e.g. not achieving a decrease in Psoriasis Area and Severity Index (PASI) score of at least 75% after adequate duration of treatment), an initially adequate response that is lost over time (secondary failure) or intolerance for the TNFα-inhibitor. The percentage of patients with an inadequate response to TNFα-inhibitors can be as high as 40-60% (Van Lümig et al 2010).

The arrival of the anti-IL 12/23 class of biological drugs provided clinicians with another treatment option (Kerdel et al 2015). Ustekinumab has shown good clinical efficacy in a Phase III study (Papp et al 2008). PASI response rates were better than those of etanercept, and efficacy was generally maintained up to 3 years after initiation of treatment (Kimball et al 2012).

More recently, a number of IL-17A and IL-17RA inhibitors are currently being investigated in Phase III studies for the treatment of a range of immune mediated inflammatory diseases (Puig 2014).

Secukinumab (AIN457) is a recombinant high-affinity fully human monoclonal anti-human IL-17A antibody of the immunoglobulin (Ig) G1/κ-class. Secukinumab binds to human IL-17A and neutralizes the bioactivity of this cytokine. IL-17A is the central cytokine of a newly defined

subset of inflammatory T cells, the Th17 cells which, in several animal models, are pivotal in multiple autoimmune and inflammatory processes. IL-17A is mainly produced by memory effector CD4+ and CD8+ T lymphocytes and is being recognized as one of the principal pro-inflammatory cytokines in immune mediated inflammatory diseases. Its neutralization is expected to treat the underlying pathophysiology of immune mediated disease, and as a consequence provide relief of (psoriatic) symptoms. Secukinumab has been shown to be superior to etanercept (Langley et al 2014) and superior to ustekinumab (Thaci et al 2015) in clearing skin of subject with moderate to severe psoriasis with a comparable safety profile.

Secukinumab has a different mode of action to TNFα-inhibitors and IL-12/23 inhibitors as it targets a different interleukin (i.e. IL17A). Secukinumab (Cosentyx®) with a recommended dose of 300 mg was approved in 2014 in Japan, and 2015 in USA, EU, Switzerland, and other countries for the treatment of moderate to severe psoriasis in adults. Secukinumab is available as a powder for solution for injection, and as a solution of 150 mg in 1 mL for injection using pre-filled syringe or a pen/auto-injector. Currently two injections (each with 150 mg) for the recommended dose (300 mg) are required. In order to allow patients to receive only one injection for the delivery of secukinumab 300 mg instead of two injections of 150 mg, Novartis is currently developing the 2 mL syringe containing 300 mg of secukinumab.

As of 25 June 2015, approximately 12,000 subjects have been enrolled in studies with secukinumab, of which 9,600 have received secukinumab at doses ranging from 0.1 mg/kg to 30 mg/kg intravenously (i.v.), and from 25 mg to 300 mg subcutaneously (s.c.), given as single or multiple doses. As of 25 June 2015, there are 79 completed and multiple ongoing trials conducted with secukinumab in indications including psoriasis, psoriatic arthritis, ankylosing spondylitis, uveitis, multiple sclerosis, rheumatoid arthritis, rheumatic polymyalgia, type I diabetes mellitus, and asthma. These studies support a favorable safety profile without indication of any specific organ toxicity. The Investigator's Brochure (IB) provides a more detailed review of the pre-clinical and clinical information on secukinumab. The aim of the present study is to assess the efficacy, safety, Pharmacokinetic (PK) parameters and local tolerability of a 2 mL pre-filled syringe of 300 mg secukinumab.

1.2 Purpose

The primary purpose of this study is to assess efficacy, safety and tolerability of 2 mL pre-filled syringe of 300 mg secukinumab. Results of this study will support the registration of secukinumab 300 mg in 2 mL pre-filled syringes.

2 Study objectives and endpoints

2.1 Primary objective

The primary objective is to demonstrate the efficacy of secukinumab 300 mg when administered as 2 mL pre-filled syringes in subjects with plaque-type psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoint) at Week 12, compared to placebo.

2.2 Secondary objective(s)

2.2.1 Key secondary objectives

- To demonstrate the efficacy of secukinumab 300 mg when administered as 2 mL pre-filled syringes in subjects with plaque-type psoriasis with respect to PASI 90 and PASI 100 at Week 12, compared to placebo.
- To demonstrate the efficacy of secukinumab 300 mg when administered as two 1 mL pre-filled syringes in subjects with plaque-type psoriasis with respect to PASI 100 at Week 12, compared to placebo.

2.2.2 Other secondary objectives

- To assess the efficacy of secukinumab 300 mg 2 mL pre-filled syringes on moderate to severe plaque-type psoriasis with respect to PASI score, IGA mod 2011 score, PASI 50 / 75 / 90 / 100 and IGA mod 2011 0 or 1 response up to Week 12 compared to placebo, and over time up to Week 52.
- To investigate the clinical safety and tolerability of secukinumab 300 mg 2 mL pre-filled syringes as assessed by vital signs, clinical laboratory variables, and adverse events (AEs) monitoring, compared to placebo.
- To assess the subject usability (ability to follow instructions for use and potential use-related hazards) and satisfaction with the secukinumab 2 mL pre-filled syringes utilizing a self-administered Self-Injection Assessment Questionnaire (SIAQ) and investigator/site staff observation of secukinumab 300 mg 2 mL pre-filled syringe administration.
- To assess the effects of secukinumab 300 mg 2 mL pre-filled syringes with respect to DLQI 0 or 1 achievement and DLQI changes at Week 12 compared to placebo, and over time up to Week 52.

3 Investigational plan

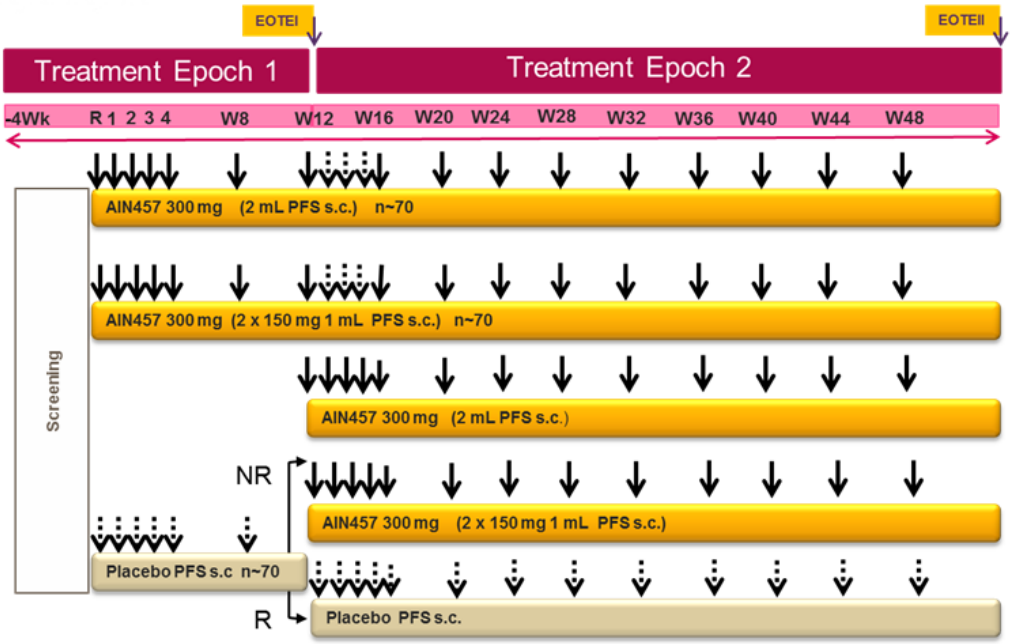
3.1 Study design

This is a 52-week multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in approximately 210 subjects with moderate to severe plaque-type psoriasis.

The study consists of 4 epochs: Screening (of at least 1 week and up to 4 weeks), Treatment Epoch I (of 12 weeks), Treatment Epoch II (of 40 weeks) and Follow-up. The treatment-free phase of 8-week should only be completed in case of early discontinuations.

Safety, efficacy and pharmacokinetic peak and trough level measurements of secukinumab will be performed according to the pre-defined visit schedule as described in Figure 3-1 and in Table 6-1.

Figure 3-1 Figure 3-2 Study design



NR = Week 12 PASI 90 Non-responder
R = Week 12 PASI 90 Responder
PFS = Pre-filled syringe

Screening (Screening to Randomization)

The screening of at least 1 week and up to 4 weeks will be used to assess eligibility of the subjects and to taper-off prohibited medication(s).

Treatment Epoch I (Randomization to Week 12 pre-dose)

The Treatment Epoch I is defined as Randomization through Visit Week 12 (prior to Week 12 dose). At the start of the Treatment Epoch I, eligible subjects will be randomized at a 1:1:1 ratio to one of three treatment groups:

- **Secukinumab 300 mg regimen group (2 mL syringe)**: one 2 mL secukinumab 300 mg plus two 1 mL matching placebo secukinumab s.c. injections once weekly for four weeks (at Randomization, Weeks 1, 2, and 3), followed by dosing every four weeks, starting at Week 4 up to Week 12.
- **Secukinumab 300 mg regimen group (1 mL syringe)**: two 1 mL secukinumab 150 mg plus one 2 mL matching placebo secukinumab s.c. injection once weekly for four weeks (at Randomization, Weeks 1, 2, and 3), followed by dosing every four weeks, starting at Week 4 up to Week 12.
- **Placebo group**: placebo secukinumab (two 1 mL s.c. injections and one 2 mL injection per dose) once per week for four weeks (at Randomization, Visits Week 1, 2, and 3), followed by dosing every four weeks starting at Week 4 up to Week 12.

For subjects who **discontinue** the study treatment prematurely for any reason before the End of the Treatment Epoch I, the End of Treatment Epoch I (EOTEI) Week 12 visit should be performed approximately four weeks after their last dose of study treatment (secukinumab or placebo). Thereafter, subjects should enter the treatment-free 8-week **Follow-up Epoch.**

Subjects will be visiting the study site at Randomization and Visits Week 1, 2, 3, 4, 8 and 12.

Treatment Epoch II (Week 12 post-dose to Week 52)

The Treatment Epoch II is defined as Week 12 through Week 52.

Prior to receiving the Week 12 dose, all subjects from the **placebo group** will be assigned to the following treatment groups based on their PASI 90 response status at Week 12.

- **PASI 90 non-responders** from the placebo group will receive at a ratio 1:1 either one 2 mL 300 mg secukinumab plus two 1 mL matching placebo **OR** two 1 mL of 150 mg secukinumab s.c plus one 2 mL matching placebo injections at Weeks 12, 13, 14, and 15, thereafter every four weeks starting at Week 16 and up to Week 48.
- **PASI 90 responders** will receive their placebo injections at Weeks 12, 13, 14, 15, and then every four weeks starting at Week 16 up to Week 48.

Subjects from the two **active groups** (who were on secukinumab since randomization) will receive placebo (one 2 mL and two 1 mL s.c. injections) at Weeks 13, 14 and 15 and continue with the treatment assigned at randomization every four weeks starting at Week 16 and up to Week 48. End of Treatment Epoch II (EOTEII) is at Week 52 and is also the end of the study.

Home administrations **(H)** of study drug are scheduled at Weeks 20, 24, 32, 36, 44 and 48.

End of Treatment Epoch II (EOTEII) is at week 52 and is also the formal end of the study. At this visit, the site should call IRT after performing the scheduled study assessments to record the completion by subject(s).

For subjects who **discontinue** study treatment prematurely for any reason before the end of the Treatment Epoch II, the End of Treatment Epoch II (EOTEII) Week 52 visit should be performed approximately four weeks after their last dose of study treatment (secukinumab or placebo). Thereafter, the subject should enter the treatment-free 8-week **Follow-up Epoch.**

Follow-up Epoch (8 weeks)

Only subjects who prematurely discontinue the treatment in Treatment Periods I or II for any reason will enter the treatment-free Follow-up Epoch to complete Visits F4 and F8 (as shown in Table 6-1).

3.2 Rationale for study design

The intent of this study is to assess a 2 mL pre-filled syringe form for the administration of 300 mg of secukinumab instead of two injections of 1 mL of 150 mg each, to psoriasis subjects that are treated with secukinumab at the recommended dose.

This 52-weeks, double-blind, randomized, parallel-group, and placebo-controlled study is using the recommended dose of 300 mg secukinumab which has been approved in Japan, USA, EU, Switzerland and other countries for the treatment of moderate to severe psoriasis in adults.

The study is in accordance with health authority guidelines and feedback on the clinical development program for the 2 mL pre-filled syringe, including the United States Food and Drug Administration (FDA) and EU agencies. The principle of a 2 mL s.c. injection is supported by a patient education document published by the National Institute of Health (NIH) that outlines the possibility to administer more than 1 mL of volume (NIH 2012). Based upon a recently conducted Novartis relative bioavailability study (CAIN457A2107) that assessed the 300 mg dose with a 2 mL s.c. injection using different devices, the pharmacokinetic data with 2 mL s.c. were similar to two marketed forms of 1 mL s.c. (pre-filled syringe and auto-injector/pen) and safety data showed no issues with 2 mL s.c. injections, including local tolerability. Therefore, it is appropriate to initiate study CAIN457A2323.

The primary endpoint of this study is at Week 12. This will allow for assessment of efficacy at a point in time for which efficacy data of current approved biologic therapies are available and which was the primary endpoint for the phase III studies with secukinumab in psoriasis, including those studies that introduced the liquid formulations (pre-filled syringe in CAIN457A2308, and auto-injector in CAIN457A2309; Blauvelt 2014, Paul 2015).

Overall, this study will assess the efficacy, PK, safety [redacted] and tolerability of secukinumab and includes a human factor analysis (including usability [ability to follow instruction for use and potential use-related hazards] and satisfaction) of secukinumab in 2 mL pre-filled syringes when used both, short-term (up to 12 weeks) and long-term (up to 52 weeks). This data will support the registration of secukinumab 300 mg in 2 mL pre-filled syringes.

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

The placebo-controlled study design was chosen to demonstrate the efficacy of 300 mg secukinumab administered as 2 mL pre-filled syringe in adult subjects suffering from moderate

to severe psoriasis compared to placebo. The selected dose regimen for this study with an initial weekly schedule up to 4 weeks followed by an s.c administration of every four weeks up to Week 48 is in line with the posology and method of administration as described in the approved product labelling. The selected design with the two injections of secukinumab 1 mL pre-filled syringes will also allow the comparison of the PK and safety profile with the secukinumab 2 mL 300 mg pre-filled syringe.

3.4 Rationale for choice of comparator

Due to the nature of psoriasis and the outcome measures for the primary and the secondary endpoints used (PASI 50, 75, 90 and 100 and IGA mod 2011 0 or 1), a placebo arm is necessary for reliable results on efficacy and safety. Moreover, the inclusion of a placebo group is in accordance with health authority guidelines (CHMP Psoriasis Guideline 2004). The duration of 3 months treatment within the placebo group up to the primary endpoint at Week 12 is accepted for the indication of plaque-type psoriasis. Subjects from the placebo group that will not achieve PASI 90 after Week 12 will receive secukinumab.

3.6 Risks and benefits

Secukinumab (Cosentyx®) 300 mg has been approved in moderate to severe psoriasis based on substantial clinical benefit and a favorable safety profile.

In total 4,546 patients with moderate to severe plaque psoriasis were included in studies in the registration program. This included 3,430 patients treated with secukinumab in 10 phase II/III studies, 2,727 of whom were treated for at least 6 months and 2,029 of whom were treated for at least 48 weeks.

Superiority of secukinumab to placebo was demonstrated for the co-primary efficacy criteria of PASI 75 and IGA mod 2011 0 or 1 at 12 weeks in all 4 pivotal placebo-controlled trials (> 62% for PASI 75 and > 48% for IGA mod 2011 0 or 1). Secukinumab was also found to be superior in efficacy compared to etanercept with a rapid onset of action in the etanercept and placebo-controlled studies, CAIN457A2302 and CAIN457A2303 and superior to ustekinumab in CAIN457A2317. The safety data from the completed and ongoing studies including AE and SAE data, laboratory parameters and immunogenicity data demonstrate a favorable safety profile. Observed risks included infections in particular upper respiratory tract infections, neutropenia and hypersensitivity reactions that can be seen with administration of foreign proteins. Most of the infections were non-serious, mild to moderate in severity, clinically easily

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

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

Fewer injection site reactions were reported with secukinumab 1 mL pre-filled syringe (containing 150 mg secukinumab), compared to etanercept, while the active treatment groups were higher vs. placebo.

In the phase III studies CAIN457A2308 and CAIN457A2309, evaluating the safety and efficacy of secukinumab in liquid formulation in the 1 mL pre-filled syringe and 1 mL pre-filled pen/auto-injector, respectively, the data showed that the PASI response with both 150 mg and 300 mg doses were superior to placebo ($p < 0.0001$). Comparing the efficacy and safety results across the phase III trials, the response rates in trials A2308 and A2309 were generally similar to those of the trials involving the lyophilized form (studies A2302 and A2303). It is expected that the 2 mL pre-filled syringe and 2 mL pre-filled pen/auto-injector are also comparable and have the same efficacy and safety profile as the liquid formulation remains the same.

A recent relative bioavailability study (CAIN457A2107) to assess the pharmacokinetic parameters, safety and tolerability of a single administration of 300 mg secukinumab administered subcutaneously (s.c.) in healthy volunteers investigated several delivery systems to identify administration options for secukinumab. The data suggest that with a “simulated” 2 mL pre-filled syringe (i.e. manual injection of 2 mL 300 mg in 10 seconds) i/ the pharmacokinetic profiles are similar to the 1 mL pre-filled syringe (with 2 injections), ii/ the tolerability (pain score) is acceptable, iii/ local reactions such as erythema, induration, hemorrhage, pruritus and leakage are minimum and finally, iv/ the safety profile is also similar to the 1 mL pre-filled syringe (with 2 x 1 mL s.c. injections). The 2 mL “simulated” form represented the best option from that study to provide the patients with a simple easy to use single-injection device for the treatment of psoriasis.

All quality, non-clinical pharmacology and toxicology data, as well as the available clinical efficacy and safety data, are considered sufficient to expect a positive benefit/risk ratio for the treatment of psoriasis with secukinumab with the 2 mL 300 mg pre-filled syringe, and therefore it is appropriate to initiate study CAIN457A2323 for registration purposes.

4 Population

Approximately 210 subjects with moderate to severe plaque psoriasis will be randomized in approximately 57 centers worldwide. Approximately 250 subjects are expected to be screened to provide the number of randomized subjects. It is also expected to randomize approximately 20% of subjects who also suffer from psoriatic arthritis. Drop-outs after randomization will not be replaced.

4.1 Inclusion criteria

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

1. Subjects must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study related activity is performed. Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations.
2. Men or women of at least 18 years of age at the time of Screening.
3. Chronic plaque-type psoriasis present for at least 6 months and diagnosed before Randomization.
4. Moderate to severe psoriasis as defined at Randomization by:
   - PASI score of 12 or greater, **and**
   - IGA mod 2011 score of 3 or greater (based on a scale of 0 – 4), **and**
   - Body Surface Area (BSA) affected by plaque-type psoriasis of 10% or greater.
5. Candidate for systemic therapy. This is defined as a subject having moderate to severe chronic plaque-type psoriasis that is inadequately controlled by
   - Topical treatment and/or
   - Phototherapy and/or
   - Previous systemic therapy

4.2 Exclusion criteria

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

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

   Note: administration of live vaccines 6 weeks prior to Randomization or during the study period is also prohibited.
4. Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor.
5. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations.

6. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
7. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the 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 subject). Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- Male sterilization (at least 6 months prior to Screening). The vasectomized male partner should be the sole partner for that subject.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: 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%), e.g. hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

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

8. Active ongoing inflammatory diseases other than psoriasis and psoriatic arthritis (PsA) that might confound the evaluation of the benefit of secukinumab therapy. Also, underlying conditions (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy. In addition, current severe progressive or uncontrolled diseases which renders the subject unsuitable for the trial or puts the subject at increased risk, including any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
9. Presence of :

- Significant medical problems, including but not limited to the following: uncontrolled hypertension (systolic ≥ 160 mmHg and/or diastolic ≥ 95 mmHg), congestive heart failure [New York Heart Association status of class III or IV].
- Serum creatinine level exceeding 2.0 mg/dl (176.8 µmol/L).
- Total white blood cell (WBC) count < 2,500/µl, or platelets < 100,000/µl or neutrophils < 1,500/µl or hemoglobin < 8.5 g/dl at Screening.

10. Active systemic infections during the last two weeks (exception: common cold) prior to randomization or any infection that reoccurs on a regular basis.
11. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold test (QFT) at Screening. Subjects with a positive or indeterminate QFT test may participate in the study if full tuberculosis work up (according to local practice/guidelines) was completed within 12 weeks prior to randomization and establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local guidelines prior to randomization.
12. Past medical history record or current infection with HIV, hepatitis B or hepatitis C prior to Randomization.
13. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for 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).
14. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
15. History or evidence of ongoing alcohol or drug abuse, within the last six months before Randomization.
16. History of hypersensitivity to any of study drug constituent.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Novartis will supply the following study drugs with the same liquid formulation:

Investigational treatment:

- Secukinumab 300 mg, provided in a 2 mL pre-filled syringe

Control treatment:

- Secukinumab 300 mg, provided as two injections of 1 mL pre-filled syringe (each 1 mL syringe containing 150 mg scekinumab)

- Secukinumab matching placebo, provided in a 1 mL or 2 mL pre-filled syringe

Secukinumab and the secukinumab matching placebo will be labeled as "AIN457 300 mg / Placebo" (2 mL) or "AIN457 150 mg / Placebo" (1 mL) to keep the blind. Subjects will be initially instructed about injections by site staff. They will receive explanations/instructions on how to self-inject the pre-filled syringe thereafter.

The removable cap of the secukinumab pre-filled syringe 1mL form only contains a derivative of natural rubber latex (note: this is not applicable to the 2 mL syringe). Although no natural rubber latex is detected in the cap, the safe use of the secukinumab 1 mL pre-filled syringe in latex-sensitive individuals has not been studied.

5.1.2 Additional treatment

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

5.2 Treatment arms

Subjects will be assigned to one of the following 3 treatment arms with 70 subjects per arm. Subjects will self-administer all secukinumab and placebo doses at study sites or at home (Table 6-1). There will always be three injections.

Subjects will be randomized using a 1:1:1 ratio into one of the treatment groups:

- **Secukinumab 300 mg regimen group (2 mL)**: one 2 mL secukinumab 300 mg plus two 1 mL matching placebo secukinumab s.c. injections once weekly for four weeks (at Randomization, Weeks 1, 2, and 3), followed by dosing every four weeks, starting at Week 4 up to Week 48. Subjects will receive three placebo injections at Weeks 13, 14 and 15.
- **Secukinumab 300 mg regimen group (2 x 1 mL)**: two 1 mL secukinumab 150 mg plus one 2 mL matching placebo secukinumab s.c. injection once weekly for four weeks (at Randomization, Weeks 1, 2, and 3), followed by dosing every four weeks, starting at Week 4 up to Week 48. Subjects will receive three placebo injections at Weeks 13, 14 and 15.
- **Placebo group**: placebo secukinumab (two 1 mL s.c. injections and one 2 mL injection per dose) once per week for four weeks (at Randomization, Visits Week 1, 2, and 3), followed by dosing every four weeks starting at Week 4 up to Week 12.

After administration of the Week 12 dose, all subjects in the placebo group will continue the treatment based on their PASI 90 response status at Week 12:

- **PASI 90 non-responders** will receive 1:1 ratio either one 2 mL 300 mg secukinumab s.c. plus two 1 mL matching placebo **OR** two 1 mL 150 mg secukinumab s.c. injections plus one 2 mL matching placebo at Weeks 12, 13, 14, 15, and then every four weeks starting at Week 16 up to Week 48.
- **PASI 90 responders** will continue on placebo (one 2 mL plus two 1 mL s.c. injections) and will receive their placebo injections at Weeks 12, 13, 14, 15, and then every four weeks starting at Week 16 up to Week 48.

5.3 Treatment assignment and randomization

At Baseline/Randomization visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the package of study drug to be dispensed to the subject. The randomization number will not be communicated to the caller.

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

If a subject discontinues before Randomization, the IRT should be notified within five days and the reason for not being randomized will be entered in the Screening Epoch Disposition electronic Case Report Form (eCRF).

Randomization will not be stratified.

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

5.4 Treatment blinding

Subjects, investigators/site personnel and Novartis clinical team reviewing data will remain blind to the identity of the treatment from the time of randomization, using the following methods: (1) randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study. (2) the identity of the treatments will be concealed by the use of investigational treatment that are all identical in packaging, labeling, appearance, and schedule of administration.

Unblinding will only occur in the case of subject emergencies (Section 5.5.9), at the time of the endpoint analysis (Section 3.5) as described below.

The blind will be kept until the final/end of study database lock.

The randomization codes associated with subjects from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until database lock.

The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason. Study treatment must be discontinued after emergency unblinding (Section 5.5.9).

5.5 Treating the subject

5.5.1 Subject numbering

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

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

5.5.2 Dispensing the study drug

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

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

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

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

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

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

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log as instructed.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

The first study treatment administration will occur at the Randomization Visit after the inclusion/exclusion criteria have been confirmed and all study scheduled assessments have been performed (except the SIAQ POST module to be completed 20-40 minutes after dosing of all three injections). All other study assessments, including blood withdrawal and completion of Patient Reported Outcomes (PROs), i.e. DLQI, [redacted] except the SIAQ POST module as applicable, should be completed prior to the self- injection of study treatment. The flow of work and the consecutive steps of assessments including Clinical Outcome Assessments (COA) are given in Section 6.

All doses of study treatment (secukinumab and/or placebo) will be self-administered by the subject either at the study site after the study assessments for the visits have been completed or at home.

The first use at Randomization and the Week 1 assessments of the self-injection will take place in the context of an observed assessment under the supervision of one site staff member. Each assessment will be conducted on a 1:1 basis. At the Randomization Visit the subjects will be instructed through the site staff by walking them through the Instructions For Use (IFU) on how to self-inject via the pre-filled syringe (IFU brochure containing detailed information about self-administration of study treatment should be provided to each subject at the beginning of the study). After providing detailed explanations/instructions, subjects will then be asked to raise any questions. Thereafter, they will proceed with self-injection. At Week 1 subjects will be asked to refer to the IFU and to proceed with self-injection of the actual study drug (i.e. without a detailed explanation/instruction on handling the syringe). During the first two self-injections at the respective visits (Randomization and Week 1) site staff will observe and complete the self-injection assessment checklist for the **2 mL syringe** (Table 6-4) at the first of the two injections at each visit. The possible hazard assessment check list (Table 6-5) will be assessed at each of the applicable visits.

Home administrations (H) should be done at pre-defined visits (Table 6-1). Home administration can be performed by subject or trained caregiver. If the subject or caregiver is not able/confident to perform home administration, the subject will be allowed to return to the site for administration of the medication. However, during those visits no additional assessments will be required.

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

Administration

The study treatment solution must be injected in **non-affected** areas of the skin.

Administration of study treatment may vary on the body regions, i.e. changing the injection site whilst **separating the 2 mL syringe and the two 1 mL syringes**.

Pre-filled syringes should be kept at 2 to 8°C (36°F and 46°F), never be frozen, and should be protected from light. Prior to administration, the boxes containing the pre-filled syringes should be allowed to adapt to room temperature unopened for about 20 minutes before

administration. Used syringes should be disposed immediately after use in a sharps container or according to the regulatory needs of the respective countries.

5.5.5 Permitted dose adjustments and interruptions of study treatment

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

5.5.6 Rescue medication

Use of rescue medication is not permitted in this study.

5.5.7 Concomitant medication

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

Any treatment known to worsen psoriasis (e.g. beta-blockers, calcium channel blockers, lithium) should be stable at least 4 weeks before randomization.

5.5.8 Prohibited medication

Use of any treatments displayed in Table 5-1 that could confound the efficacy of the investigational drug is **NOT** allowed during the study for any indication. After Screening, the use of concomitant medication for psoriasis in all body regions is restricted to bland emollients (not supplied by Novartis) and other non-medicated interventions. Use of bland emollients must be recorded on the Concomitant Medications eCRF and should be avoided during the 12 hours preceding a scheduled visit. Use of any other non-medicated interventions should be recorded in the eCRF.

A mild to moderate potency topical corticosteroid (TCS) will be allowed for the treatment of the face, scalp, and anogenital area during the Screening Epoch. These TCS should be stopped at least the day before the Randomization Visit.

The investigator should instruct the subject to notify the study site about any/all new/additional treatments after starting the study drug administration. Prior to starting the study, all prohibited treatments should be washed out as shown in Table 5-1 below. At the discretion of the investigator, if any use of a prohibited treatment presents an undue safety risk for the subject, the study treatment should be discontinued. If a live vaccination has to be administered, the study treatment should be discontinued.

Table 5-1 Prohibited medication by period/epoch (for any indication)

Prohibited medication[a, b]	**Washout period (before randomization)**
Alefacept, briakinumab, efalizumab, ustekinumab	24 weeks
Biological immunomodulating agents other than above (e.g., adalimumab, etanercept, infliximab)	12 weeks
Other systemic immunomodulating treatments[c] (e.g. Methotrexate, cyclosporine A, corticosteroids[c], cyclophosphamide)	4 weeks
Other systemic psoriasis treatments[d] (e.g. retinoids, fumarates, apremilast)	4 weeks
Photochemotherapy (e.g., PUVA)	4 weeks
Phototherapy (e.g., UVA, UVB)	2 weeks
Topical treatment that is likely to impact signs and symptoms of psoriasis (e.g. potent corticosteroids [CS], vitamin D analogues, pimecrolimus, tacrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tar, urea, α-hydroxy or fruit acids)[e, f]	2 weeks
Live virus vaccinations***	6 weeks
Any investigational treatment (including IL23p19) or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)

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

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

[c] Oral, i.v., i.m., s.c., intra-articular, peri-articular. Exception: inhalative corticosteroids (CS) with only a topical effect (e.g., to treat asthma) are not considered "**systemic** immunomodulating treatments" and are therefore acceptable as co-medication.

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

[e] Mild to moderate topical corticosteroids (TCS) are allowed only during the **Screening Epoch** if used only on the face, scalp and/or anogenital area and should be stopped the day before the Randomization visit.

[f] Topical corticosteroids (mild to moderate) and other topical treatments will be allowed during **Treatment Epoch II ONLY** if (all must apply):

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

*** Inactivated virus vaccinations are allowed

Exposure to light

Exposure to ultraviolet (UV) light (including sunbathing and/or use of UV tanning devices) should be limited to avoid possible effect on psoriasis.

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency

condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and an e-mail with an onscreen display of the medication confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

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

- Protocol number
- Study drug name (if available and applicable)
- Subject number

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

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

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A subject will be considered to have completed the study when the subject has completed the last visit planned in the protocol (Visit Week 52 or Visit F8).

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

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

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

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

Study treatment must be discontinued under the following circumstances:

- Subject wish
- Withdrawal of consent
- Emergence of the following AEs: AEs that in the judgment of the investigator/qualified site staff, taking into account the subject's overall status prevent the subject from continuing study treatment.

- Any laboratory abnormalities that in the judgment of the investigator/qualified site staff, taking into consideration the subject's overall status, prevent the subject from continuing study treatment.
- Pregnancy (Section 6.5.6 and Section 7.6)
- Ongoing use of prohibited treatment as shown in Table 5-1
- Any situation in which study participation might result in a safety risk to the subject
- Emergency unblinding

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

At the time of the study treatment discontinuation visit, if it has been approximately 4 weeks post last dose of study treatment then the assessments described in EOTEI **OR** EOTEII should be completed at this visit.

If it has not been approximately 4 weeks post last dose of study treatment at the time of the study treatment discontinuation visit, then the subject should be scheduled to return 4 weeks post last dose for their EOTEI assessments **OR** EOTEII assessments.

The investigator/qualified site staff must contact the IRT when the subject completes the EOT Visit Week 12/EOTEI **OR** Week 52/EOTEII assessments to register the subject's early completion of the study due to study treatment discontinuation.

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

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

- New/concomitant treatments
- Adverse events/serious adverse events

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

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

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

5.6.2.1 Discontinuation from a treatment-free period

If premature withdrawal occurs for any reason in the treatment-free period (within the four weeks after last dose or in the 8-week Follow-up Epoch), the investigator must make every

effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the applicable end of study eCRF (i.e. F8).

In Section 6 assessments for subjects who discontinue from the Follow-up Epoch are shown.

5.6.3 Withdrawal of informed consent

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

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

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

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

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

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

5.6.4 Loss to follow-up

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

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrollment). Should this be necessary, the subject must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will

be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists assessments that are recorded in the clinical database. Assessments that are source documentation only will not be entered into the eCRF. Data reflecting to which inclusion/exclusion criteria are not met are captured on the Inclusion/Exclusion eCRF.

Subjects should be seen for all visits on the designated day or as closely as possible to the original planned visit schedule (Table 6-1). Every effort should be made to respect the timeframe for all visits and particularly when PK samples are collected.

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

If a subject re-screens for the study, then the subject must sign a new ICF and be issued a new subject number prior to any screening assessment being conducted for the subject under the new screening subject number. For all subjects, the investigator/qualified site staff will record if the subject was re-screened on the re-screening eCRF and any applicable screening numbers the subject was issued prior to the current screening number. The date of the new informed consent signature must be entered on the Informed Consent eCRF to correspond to the new screening subject number. For re-screening, all screening assessments must be performed per protocol, except for the tuberculosis (TB) work up and chest x-ray, if applicable, if performed not more than 12 weeks before randomization.

For subjects who discontinue study treatment prematurely before the end of the treatment epoch for any reason other than withdrawal of informed consent or loss to follow-up procedures as described in Section 5.6 should be followed.

During Treatment Epochs I and II, subjects may be seen at an unscheduled visit, e.g. if they experience deterioration of psoriasis, or AEs that in the opinion of the investigator need intervention or repeated laboratory testing. During these unscheduled visits, study treatment will **NOT** be administered. The assessment(s) performed at an unscheduled visit are at the investigator's discretion.

Order of assessments:

Guidance for the order of assessments as shown in Table 6-1 is as follows (may vary depending on different type of visits):

Subjects

- Subjects should usually complete the subject-reported outcome (PROs/ePROs) assessments (i.e. DLQI [redacted]) prior to any investigator assessments.

Investigator / Qualified Site Staff

1. IGA mod 2011
2. PASI
3. Other procedures

- All remaining study visit procedures (e.g. laboratory and PK sample collection, vital signs measurements) must be completed prior to study treatment administration.
- Enter PASI and IGA mod 2011 assessments into eCRFs BEFORE contacting IRT at Randomization Visit and EOTEI Visit Week 12.
- Contact IRT to register the subject visit.
- Prepare the corresponding study medication packs and allow to adapt to room temperature for about 20 minutes before administration (dispense for home administrations, as required).
- Provide guidance to subjects for self-administration prior to the first treatment administration (Section 5.5.4) at Randomization; from Visit Week 1 until End of Treatment Epoch II subjects should refer to the Instructions For Use (IFU) and proceed with self-administrations either at the site or they receive instructions for sub-sequent home administrations (H).
- SIAQ PRE module should be performed once at Randomization
- Subject self-administration assessment
- Pre-filled syringe usability and hazard assessment should be done by site personnel, at Randomization Visit and at Visit Week 1
- SIAQ POST module, as shown in Table 6-1

Table 6-1 Assessment schedule

Epoch	**Scr**	**Treatment Epoch I**							**Treatment Epoch II**														***FU EPOCH***[c]		**U**
Week (Relative to Randomization)	≤ - 4	**R**[i]	1	2	3	4	8	12[a] **EOTEI**	13	14	15	16	20 **H**	24 **H**	28	32 **H**	36 **H**	40	44 **H**	48 **H**	52[b] **EOTEII**	**F4**	**F8**[b]	
Day	≤ - 28 to ≥ - 7	R	8	15	22	29	57	85	92	99	106	113	141	169	197	225	253	281	309	337	365	*393*	*421*	
Obtain informed consent	X																							
Subject demographics	X																							
Inclusion/exclusion criteria[d]	S	S																						
Smoking history	X																							
Psoriasis medical history/ Previous psoriasis therapies	X																							
Cardiovascular medical history	X																							
Medical history and prior medications	X																							
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X			X			X			X	X	X	X
Physical Examination[d]	S	S						S				S			S			S			S	S	S	S
Height	X																							
Weight	X	X																			X			X
Vital signs	X	X				X	X	X				X			X			X			X	X	X	X
Lab analysis: safety panel[e]	X	X				X	X	X				X									X		X	X
Fasting labs: glucose, lipid panel, high sensitivity CRP[e]		X																						
Urinalysis (local)	X																							

Epoch	**Scr**	**Treatment Epoch I**							**Treatment Epoch II**													**FU EPOCH**[c]		**U**
Week (Relative to Randomization)	≤ -4	R[i]	1	2	3	4	8	12[a] **EOTEI**	13	14	15	16	20 **H**	24 **H**	28	32 **H**	36 **H**	40	44 **H**	48 **H**	52[b] **EOTEII**	**F4**	**F8**[b]	
Day	≤ -28 to ≥ -7	R	8	15	22	29	57	85	92	99	106	113	141	169	197	225	253	281	309	337	365	*393*	*421*	
QuantiFERON® TB-Gold In-Tube test[e]	X																							
Serum pregnancy test[e]	X																							
Urine pregnancy test (local)[f]		X																			X			X
ECG (standard 12 lead)	S																							
Blood sample for PK[g,k,l,e]		X				X		X	X	X	X	X			X						X			X
PASI	X	X	X	X	X	X	X	X				X			X			X			X		X	X
BSA	X	X																						
IGA mod 2011	X	X	X	X	X	X	X	X				X			X			X			X	X	X	X
DLQI		X						X							X						X		X	X
SIAQ[h]		X	X			X	X	X							X						X		X	X
Usability and hazard assessment		X	X																					
Adverse event (SAE/AE) assessment[j]	X	X	X	X	X	X	X	X	X	X	X	X			X			X			X	X	X	X

Epoch	**Scr**	**Treatment Epoch I**							**Treatment Epoch II**														***FU EPOCH***[c]		**U**
Week (Relative to Randomization)	≤ - 4	R[i]	1	2	3	4	8	12[a] **EOTEI**	13	14	15	16	20 **H**	24 **H**	28	32 **H**	36 **H**	40	44 **H**	48 **H**	52[b] **EOTEII**	**F4**	**F8**[b]	
Day	≤ - 28 to ≥ - 7	R	8	15	22	29	57	85	92	99	106	113	141	169	197	225	253	281	309	337	365	*393*	*421*	
Administration of study treatment at site		X	X	X	X	X	X	X	X	X	X	X			X			X						
Home administration (H)[m]													H	H		H	H		H	H				
Randomization and supply order by IRT[a]		X	X	X	X	X	X	X	X	X	X	X			X			X						X
Screening period eCRF completion		X																						
EOTEI eCRF completion								X																
EOTEII eCRF completion																					X			
EOF eCRF completion																							X	

AE = adverse event, **BSA** = Body Surface Area**, CRP** = high sensitivity C-reactive protein, **DLQI** = Dermatology Life Quality Index, **eCRF** = electronic case report form, **EOF** = End of Follow-up, **EOTEI** = End of Treatment Epoch I, **EOTEII** = End of Treatment Epoch II, **FU** = Follow up, [redacted] **H** = home administration (self-injection or trained caregiver), **IGA mod 2011** = Investigator's Global Assessment modified 2011, [redacted], **IRT** = Interactive Response Technology, **PASI** = Psoriasis Area and Severity Index, **PK** = Pharmacokinetics, **R** = randomization, **SAE** = serious adverse event, **Scr** = screening, **SIAQ** = Self-Injection Questionnaire, **S** = assessment only recorded in source documentation, **U** = unscheduled visits - assessments performed at unscheduled visits are at investigator's discretion; **X** = assessment entered or transferred into the clinical data base

[a] During Visit Week 12, subjects will have their last assessments performed for the Treatment Epoch I prior to the dose at this visit.

[b, c] At Visit Week 52, subjects will have their last assessments performed for the Treatment Epoch II which is also the formal end of the study. Visit Week 12 (**EOTEI**) must be completed for treatment **discontinuations** from the **Treatment Epoch I** and Visit Week 52 (**EOTEII**) must be completed for treatment **discontinuations** from **Treatment Epoch II**; **all discontinuations should then continue with their corresponding Follow-up Visits F4 and F8**. **A Follow-up Epoch is not needed for subjects who complete the study up to Visit Week 52; completers have their last visit at Week 52**.

[d] These assessments are source documentation only and will not be entered into the eCRF. However, data regarding to which inclusion/exclusion criteria are not met are captured on the Inclusion/Exclusion Screen eCRF.

[e] Samples will be shipped to and analyzed by the central laboratory

[f] If there is a positive urine pregnancy test, study treatment must be withheld and a serum pregnancy test must be done at the same visit. A urine pregnancy test is not required for a woman who is sterile or who is not of childbearing potential.

[g] Samples will be shipped by the sites and stored by the central laboratory. A shipment to reference laboratories for analysis will be done by the central laboratory. **Detailed sampling intervals for PK [redacted] are shown in Appendix 2** in **Table 14-1 and Table 14-2**.

[h] SIAQ PRE module only at Randomization, SIAQ POST module for all SIAQ time points

[i] The PASI Score and IGA mod 2011 eCRFs must be completed prior to contacting IRT for randomization. At Randomization Visit, the investigator must confirm subject meets IGA mod 2011, PASI and BSA eligibility per these eCRFs before randomizing the subject. At EOTEI Visit Week 12, the site must have the PASI 90, see a) and b) responder status from the PASI Score eCRF available for entry into IRT.

[j] Adverse events that my occur at home administrations as well as concomitant medication should be collected by the investigator and reported in the eCRF

[k] An unscheduled [redacted] PK sample is collected only to replace [redacted] PK sample not taken at a regular scheduled visit. In case an unscheduled [redacted] sample is taken, there should always be a matching unscheduled PK sample taken at the same time point (both pre-dose).

[l] Blood withdrawals for PK sampling: pre-dose samples at Randomization, Weeks 4, 12, 13, 14, 15, 16, 28; one last pre-dose blood withdrawal for PK is scheduled at Week 52. An additional pre-dose sample should be withdrawn in case of early discontinuations at Visit F8 or if an unscheduled visit (U) is conducted **Appendix 2** in **Table 14-1**.

[m] Home administrations can be performed by subject or caregiver. If the subject or caregiver is not able/confident to perform home administration, the subject will be allowed to return to the site for administration of the medication.

6.1 Information to be collected on screening failures

Subjects who sign the Informed Consent Form (ICF) and discontinue prior to randomization at the Randomization Visit are considered screening failures.

If a subject discontinues before entering the double-blind Treatment Epoch I, the IRT must be notified within five days and the reason for not being randomized will be entered in the Screening Epoch Disposition electronic Case Report Form (eCRF). The Screening Visit date, the Demography eCRF, Informed Consent eCRF, Inclusion/Exclusion Criteria eCRF and Subject re-screening eCRF should be completed. The Adverse Event eCRF and a SAE Form should be completed for any serious adverse event (SAEs) that occurred during the Screening Epoch. The Withdrawal of consent eCRF should be completed if consent was withdrawn prior to the randomization. The Death eCRF should be completed in the case of a death during the Screening Epoch.

All subjects who have signed the Informed Consent Form but not entered into the next treatment epoch will have the study completion page for the Screening Epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. For all subjects who have signed the Informed Consent Form and entered the Treatment Epochs I and II of the study, adverse events **occurring after informed consent was signed-off** should be recorded on the Adverse Event eCRF.

6.2 Subject demographics/other baseline characteristics

6.2.1 Demographics

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

6.2.2 Psoriasis medical history/previous psoriasis therapies

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

- The date of first diagnosis of plaque-type psoriasis
- The date of first diagnosis of other locations or clinical forms of psoriasis, e.g.:
  - Generalized pustular or pustular palmoplantar psoriasis
  - Guttate, palmoplantar, nail, inverse, scalp or erythrodermic psoriasis
- The previous treatments of psoriasis (including previous use of biologic therapies, as well as phototherapy and/or photochemotherapy) and the reason for discontinuation
- The presence of psoriatic arthritis and date of first diagnosis

6.2.3 Smoking history

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

6.2.4 Co-morbidities – cardiovascular medical history

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

6.2.5 Relevant medical history/current medical conditions

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

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

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

6.2.6 Determination of the tuberculosis status

Determination of the tuberculosis (TB) status should be done at Screening and should be performed as defined by local guidelines. The TB status must be determined by medical history, signs, symptoms, TB testing (QuantiFERON-TB Gold assay). Any significant findings should be recorded in the TB assessment eCRF and the Medical History eCRF, as deemed necessary.

QuantiFERON TB-Gold In-Tube assay

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

Positive or indeterminate tests must be recorded on the Tuberculosis assessment eCRF; the workflow of sample handling in case of positive or indeterminate test results is provided in Figure 6-1.

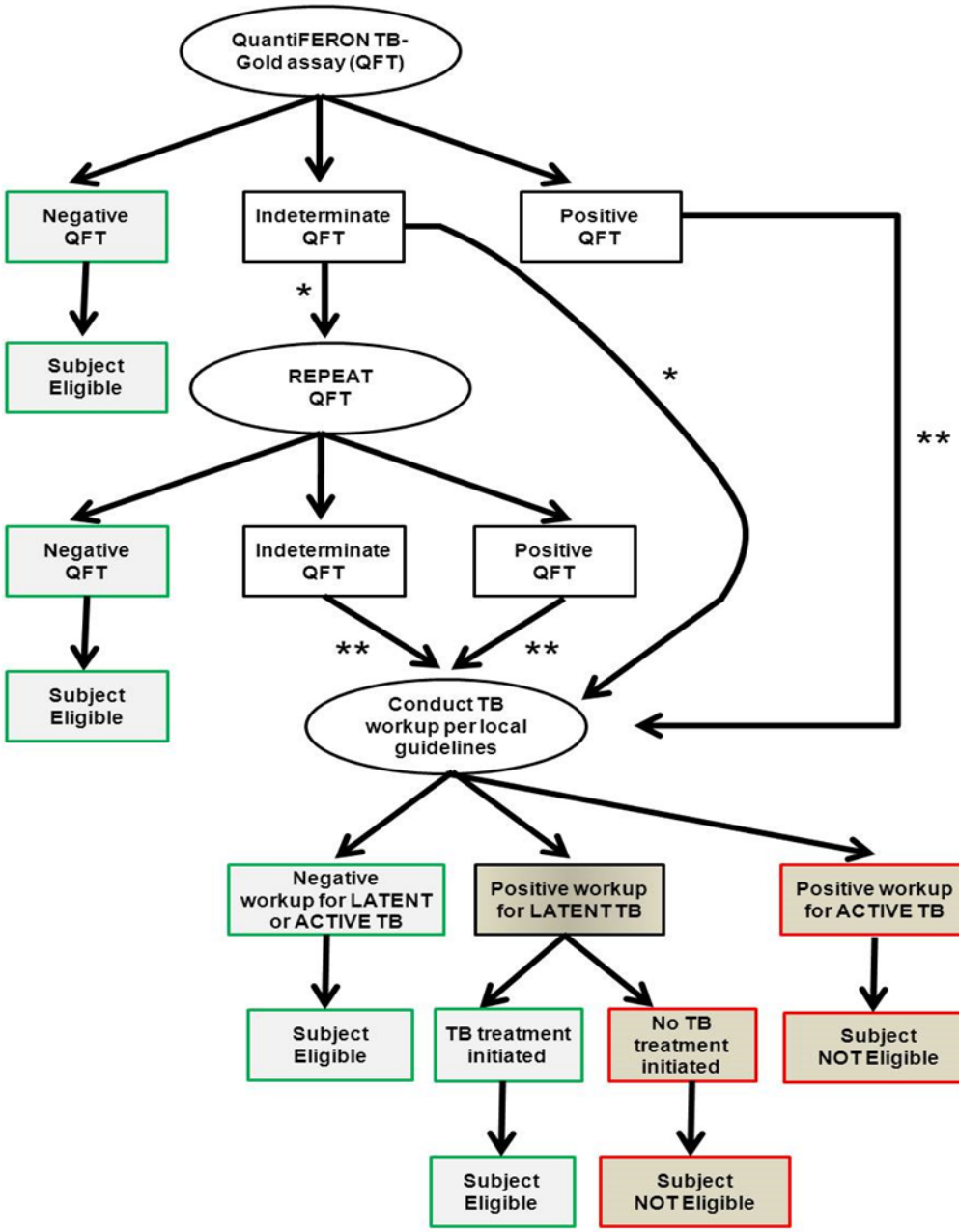
- If the test result is **negative**, the subject may be randomized.
- If the test result is **positive**, the investigator should perform a work-up for the test result as per local procedures. If a TB work-up was conducted prior to the screening of the subject,

results of the work-up can be used to assess eligibility if the work-up was conducted within 12 weeks prior to randomization.

- Subjects **positive** for latent TB per work-up may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration. Subjects positive for active TB per work-up are not eligible for the study. Subjects negative for TB (no signs of latent or active TB) per work-up may be randomized to the trial.

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

Figure 6-1 Tuberculosis screening flowchart



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

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

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

6.2.7 Other baseline characteristics

Assessments at baseline are shown in table 6-1.

6.3 Treatment exposure and compliance

All doses of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page (visit specific and summary pages). Compliance to the planned site administration schedule is expected to be high since the study treatment will be administered in the presence of the investigator or study personnel at pre-defined visits. Compliance will also be assessed and confirmed by a field monitor by drug accountability logs, by documentation and information provided by IRT and by the qualified site personnel that is responsible for treatment dispensation, preparation, administration and accountability. Cross-checks should be performed in case of home administrations (H) and empty medication boxes/outer packing/devices should be collected for compliance checks by field monitors.

6.4 Efficacy

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

- Investigator's Global Assessment modified 2011 (IGA mod 2011; scale from 0 – 4)
- Psoriasis Area and Severity Index (PASI; score from 0 – 72)

6.4.1 Investigator Global Assessment (IGA mod 2011)

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

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

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

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

Table 6-2 The IGA mod 2011 rating scale

Score	Short Description	Detailed Description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present.
1	Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling.
2	Mild	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling.
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling.

4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe/coarse scaling covering almost all or all lesions.

Note: Involvement of nails is not part of the assessment

Based on this scale, the following criteria apply:

- A subject will be eligible to participate in the study if she/he has an IGA mod 2011 score at the Randomization Visit of 3 or 4.
- A subject will be considered as IGA mod 2011 0 or 1 responder if she/he achieves a score of 0 or 1, and improved by at least 2 points on the IGA scale at a given time point compared to baseline.

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

The investigator or qualified designee will complete the PASI assessment as indicated in Table 6-3. Whenever possible, PASI assessments should be performed by the same evaluator throughout the study.

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

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

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

Table 6-3 The PASI scoring system

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

* Percentage (not score) of body region (not whole body) affected will be entered in the eCRF
† Neck is assessed as part of the Head (H) body region.
‡ Axillae and groin are assessed as part of the Trunk (T) body region.
§ Buttocks are assessed as part of the Lower limbs (L) body region.

The following definitions used in this study are based on CHMP guidelines for psoriasis (CHMP/EWP/2454/02 2004) to assess efficacy in conjunction with Investigators's Global Assessment (IGA mod 2011):

- **PASI 50 response:** subjects achieving ≥ 50% improvement (reduction) in PASI score compared to BSL are defined as PASI 50 responders
- **PASI 75 response**: subjects achieving ≥ 75% improvement (reduction) in PASI score compared to BSL are defined as PASI 75 responders

- **PASI 90 response**: subjects achieving ≥ 90% improvement (reduction) in PASI score compared to BSL are defined as PASI 90 responders
- **PASI 100 response/remission**: complete clearing of psoriasis (PASI=0)
- [redacted]

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

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

Further details regarding the formula are provided in Table 6-3.

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

The PASI 90 responder status of all subjects will be calculated at the end of Treatment Epoch I, at Visit week 12.

[redacted]

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 subject's body area is affected by the disease, is mandated by the EMA for the clinical investigation of medicinal products for the treatment of psoriasis (CHMP/EWP/2454/02 2004).

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

6.5 Safety

Blood withdrawals and safety assessments should be done prior to study treatment administration and should be taken as shown in Table 6-1 and in Appendix 2, Table 14-2. Appropriate safety assessments (e.g. evaluation of AEs and SAEs including injection site reactions) should be repeated after the dose is administered (Section 7).

6.5.1 Physical examination

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

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

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

6.5.2 Vital signs

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

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

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

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

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

6.5.3 Height and weight

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

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

6.5.4 Laboratory evaluations

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

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

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

6.5.4.1 Hematology

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

6.5.4.2 Clinical chemistry

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

6.5.4.3 Fasting laboratory evaluations

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

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

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

6.5.4.3.1 High sensitivity C-reactive protein

High sensitivity C-reactive protein (hsCRP) will be assessed using a fasting blood sample at baseline as indicated in Table 6-1.

6.5.4.3.2 Lipid panel

A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), total cholesterol and triglycerides will be measured from a fasting blood sample at Baseline/Randomization as indicated in Table 6-1.

6.5.4.3.3 Glucose

Glucose will be assessed as indicated in Table 6-1.

6.5.4.4 Urinalysis

Dipsticks will be provided by the central laboratory to the study sites for local urinalysis assessments. Standard dipstick measurements for specific gravity, protein, glucose, pH, blood, urine blood dipstick (non-hemolyzed), urine blood dipstick (hemolyzed), bilirubin, ketones and WBC will be done at scheduled visits as indicated in Table 6-1. If needed conditional microscopy assessments will be optional.

[redacted]

6.5.5 Electrocardiogram (ECG)

A standard single 12-lead ECG will be collected at Screening. The investigator/qualified site staff must review and initial the tracing. The original ECGs appropriately signed, should be collected and archived at the study site.

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

ECG tracing filed in the study site source documents. ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Although there is no exclusion criterion based on ECG results, the ECG at Screening must be reviewed for major abnormalities prior to enrollment into the study.

Clinically significant abnormalities should be recorded on the relevant section of the Medical History/Cardiovascular History/Current medical conditions/AE eCRF page as appropriate.

6.5.6 Pregnancy

A serum β-hCG test will be performed at Screening in all pre-menopausal women who are not surgically sterile. In addition, all women who are not sterilized or are of childbearing potential at Screening, a local urine pregnancy test must be performed as indicated in Table 6-1.

Any woman with a confirmed positive pregnancy test during Screening is not eligible for randomization. A positive urine pregnancy test during the treatment epochs of the study requires immediate interruption of study treatment until a serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, the subject must be discontinued from the study after follow-up assessments have been performed.

6.5.7 Appropriateness of safety measurements

The safety assessments selected are standard measures for a biologic immunomodulating agent in Psoriasis.

6.6 Other assessments

The following additional assessments will be performed:

- Clinician Reported Outcomes (ClinRO):
  Usability and hazard assessment of the pre-filled syringe
- Patient Reported Outcomes – (PRO)
  Subject satisfaction assessment of Self-Injection Questionnaire (SIAQ)
  Dermatology Life Quality Index (DLQI)
  [redacted]
- Pharmacokinetics

6.6.1 Clinical Outcome Assessments (COAs)

6.6.1.1 Clinician Reported Outcomes (ClinRO)

6.6.1.1.1 Usability and hazard assessment of the pre-filled syringe (**2 mL syringe**)

The goal is to measure and evaluate the usability of the pre-filled syringe during observed use. The assessment of the ability to follow the Instructions For Use (IFU) will be performed for the first of the 2 mL injection at the two respective visits as well as the assessment of the hazards will be performed as a summary assessment for the 2 mL injection.

Subjects will be instructed at Randomization through the site staff on how to self-inject via pre-filled syringes following the Instructions For Use (IFU). After explanations/instructions given at the Randomization Visit, the injection will be self-administered by the subject into the appropriate injection site of the body. The delivery of the dose will be observed by investigator/site staff based on observation check lists at Randomization and Visit Week 1 together with an assessment of potential administration hazards based on identified hazards list as well as non-directed querying for any observed problems during self-injection (Table 6-5).

Primary usability assessment:

- Assessment of successful **self-administration by the subject** at Visit Week 1, by studying the number and percentage of subjects who successfully perform this self-injection (note: **without** prior explanations/instructions at this visit, as this has been performed prior to dosing at Randomization only). Successful self-injection is achieved when the subject performs all required steps effectively and safely to deliver the correct dose from the device at the correct injection site. The sequence of user steps as per IFU being minimally required are 1) removing the needle cap; 2) pinch the skin at injection site; 3) insert needle into skin; 4) hold onto the finger flange; 5) fully depress plunger until end point; 6) hold the device in position for 5 seconds. As per Table 6-4 below, these 6 critical steps will be used to define successful administration. The general passing usability goal for 'successful use' task completion will be defined as ≥ 90% pass rate of following these steps.

Secondary usability assessment:

- Assessment of **subject use errors** that occur during the First Use at Randomization (after providing initial explanations/instructions) and repeated self-injection at Visit Week 1 (without a detailed explanation/instruction on handling the new form) by investigating the frequency of observed or reported difficulties in completing the self-injection after initial explanations/instructions and self-injection without explanations/instructions after a time lag that represents standard treatment. The number and percentage of subjects who successfully complete each of the indicated steps as per the IFU (Table 6-4 self-injection assessment check list) as well as the number and percentage of subjects who experience any of the defined possible hazards (based on identified hazards list) as well as non-directed querying for any observed problems during self-injection (Table 6-5) will be computed by visit.

- Assessment of successful First Use by subject after initial explanations/instructions, by studying the number and percentage of subjects at Randomization who successfully perform the self-injection as defined above for the primary usability assessment.

The First Use at Randomization and the Week 1 assessments will take place in the context of an observed assessment under the supervision of one site staff member. Each assessment will be conducted on a 1:1 basis. At the Randomization visit the subjects will be instructed through the site staff by walking them through the Instructions For Use (IFU) on how to self-inject via pre-filled syringe. Subjects will then be asked to raise any questions if they have any. Thereafter, they should proceed with self-injection. At Visit Week 1 subjects will be asked to refer to the IFU and to proceed with self-injection of the actual study drug (i.e., without providing explanations/instructions). During the first self-injections at the respective visits (Randomization and Week 1) site staff will observe and complete the self-injection assessment checklist (Table 6-4) at the first of the injections at each visit (for the 2 mL form). The possible hazard assessment check list (Table 6-5) will be assessed for the injections at each of the applicable visits for the 2 mL form. The primary usability variables will be assessed based on binary (performed correctly: yes/no) response for the self-injection assessment check list (Table 6-4). The possible hazard check list variables will be mainly assessed based on binomial (**occurred**: yes/no) response. Additionally, responses from the directed and non-directed querying for any observed problems and specification thereof during self-injection will be analysed on a case by case basis. For each item of the assessment checklists, the number and percentage of subjects with each response will be summarized. Where relevant, the number, percentage, average, standard deviation, minimum and maximum shall be presented.

Table 6-4 Self-injection assessment check list (2 mL syringe)

No.	IFU indicated steps	Required to be completed for successful administration
P1	Washed hands with soap and water	No
P2	Cleaned the injection site	No
P3	Removed the safety syringe from the outer box	No
P4	Took syringe out of the tray	No
P5	Checked expiration date on syringe label	No
P6	Inspected the safety syringe for damage	No
P7	Inspected liquid for brown discoloration or particles	No
P8	Removed needle cap from safety syringe	Yes
P9	Discarded needle cap	No
P10	Pinched the skin at injection site	Yes
P11	Inserted the needle into skin	Yes
P12	Held onto the finger flange	Yes
P13	Fully depressed plunger until end point	Yes
P14	Held plunger pressed fully down and syringe in place for 5 seconds	Yes
P15	Kept plunger fully depressed while lifting the needle straight from injection site	No
P16	Released the plunger	No

No.	IFU indicated steps	Required to be completed for successful administration
P17	Allowed syringe guard to automatically activate and cover the needle	No
P18	Disposed used safety syringe in a sharps container	No

Table 6-5 Possible hazard assessment check list (2 mL syringe)

No.	Possible Use related hazards
H1	Was there a needle stick in a critical area (e.g. eye, carotid artery)?
H2	Was there a needle stick in a non-critical area[1]?
H3	Was any part of the device swallowed? If yes, please specify.
H4	Was an immediate type allergic reaction noticed to device material?
H5	Was increased pain noticed by the patient due to bent needle?
H6	Was there breakage of the device observed?[2]
H7	Was swallowing of material debris observed?[3]
H8	Was any other problem observed?[3]
H9	Was less than the full dose administered?[4]

[redacted]

[1] Excluding the actual injection into the appropriate injection site of the body
[2]If yes, then it is to be specified under which circumstances breakage occurred and which parts were affected, as well any additional problems (e.g. injuries) due to the breakage are to be described.
[3]If yes, then it is to be specified. Possible events might include: irritated skin; drug too cold when injected; the drug or device upon visual inspection appeared unsuitable for injection; intradermal instead of subcutaneous injection; and other events.
[4]If yes, then it is to be specified why, e.g. leakage from injection site, early removal.

During the self-injection the observing site staff member must exercise judgment and intervene in the self-administration should a subject not be acting in a safe or reasonable manner, or any manner which does not fall within the scope of the study objectives, including but not limited to:

a. In the event that a subject performs (or is judged to be about to perform) a use error which could pose a risk to the health or well-being of a subject the observing site staff member will pause the subject to point out the error and decide whether it is better to terminate the self-injection. If in his or her judgment the self-injection can continue, he or she will correct the subject's usage of the product and notify the subject to recommence at the same point. Any such use error will be documented.
b. If there is, or appears to be, any risk of a health and safety incident including injury to any party. It is likely that this will require the self-injection to be terminated at the discretion of the observing site staff member.

Any pre-filled syringe for which a defect or malfunction is noticed prior to or during the injection at any of the study visits, must be kept at the site until guidance is received from

Novartis on whether it should be returned to Novartis or discarded. Additionally, from Visit Week 2 onwards, any noticed defect, malfunction, and problem during the injections or product complaints with the pre-filled syringe should be recorded in the source document by the site, detailing the issue, the date and the visit number. It should also be reported to Novartis. Similarly, during Treatment Epochs I and II, if such defects, malfunctions, problems during injections or product complaints are noticed by subjects during home administration, they must immediately be reported back to the sites, documented in detail in the source documents and reported to Novartis.

6.6.1.2 Patient Reported Outcomes (PRO)

6.6.1.2.1 Subject satisfaction assessment of Self-Injection Questionnaire (SIAQ) – **2 mL syringe**

The Self-Injection Assessment Questionnaire (SIAQ) measures the overall subject experience with subcutaneous self-injection, and to investigate the psychometric properties (Keininger and Coteur 2011, Appendix 4). The SIAQ will be performed as a summary assessment for the 2 mL syringe at the visits as outlined in the visit schedule (see Table 6-1).

The **SIAQ PRE module** is to be self-completed before the first self-injection at Randomization. The **SIAQ POST module** is to be completed following the self-injections as the visits indicated in Table 6-1, including Randomization. The PRE module includes 7 items grouped into three domains: Feelings about injections, Self-confidence and Satisfaction with self-injection, the POST module includes several items addressing four principal domains: Feelings about injections, Self-confidence, Injection-site reactions, Ease of use plus a single item assessing Self-image (see Table 6-1).

The two modules of the SIAQ should be completed by subjects while alone in a quiet environment. The PRE module is completed immediately before the first self-injection and the POST module is completed 20-40 minutes after dosing (three injections). There is no stipulated recall period for the SIAQ, because the recall period varies from one domain to another. For example, items from the injection-site reaction burden domain refer to the subject's experience during or after the injection, whereas items from the general feelings about injections domain refer to general attitudes. Subjects should rate each item of the SIAQ on a 5-point semantic Likert-type scale, where a score of 1 corresponded to the subject's worst experience and a score of 5 corresponds to the subject's best experience. Item scores will be transformed to obtain a score ranging from 0 (worst experience) to 10 (best experience) for each item. The domain score will be the mean of the item scores included in the domain. Domain scores will be calculated only if at least half of the domain items were completed.

The SIAQ questionnaire (date of publication 2011) will be completed by the subject as indicated in Table 6-1.

6.6.1.2.2 Health-related quality of life (HRQOL) questionnaires

The impact of psoriasis on various aspects of subject's health-related quality of life (HRQOL) will be assessed by the following validated instruments:

- Dermatology Life Quality Index (DLQI)

- [redacted]

These questionnaires should be completed by subjects **before** they see the study physician (investigator or designee) who will perform the investigator assessments.

All questionnaires will be completed in the language the respondent is most familiar with, at the scheduled visit before the subject sees the investigator for clinical assessments. The subject should be given sufficient space and time to complete the questionnaires. The study coordinator should check the questionnaires for completeness and encourage the subject to complete any missing responses.

Completed questionnaires will be reviewed and examined by the investigator only after the clinical efficacy assessments (PASI, IGA mod 2011 [redacted]), for responses that may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the subject. If AEs or SAEs are confirmed then the investigator must record the events as per instructions given in Section 7 of the protocol. Investigator should not encourage the subject to change the responses reported in the completed questionnaires.

Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item general dermatology disability index designed to assess health-related quality of life in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral warts (Finlay and Khan 1994, Appendix 5). The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 32 different skin conditions and is available in 55 languages. The recall period is the last week, and the instrument requires 1 to 2 minutes for completion.

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

The purpose of the DLQI in this study is to investigate the effects of treatment of secukinumab with respect at Week 12, compared to placebo, and over time up to Week 52, compared to placebo.

The DLQI questionnaire (version 2, date of publication 1994) will be completed by the subject as indicated in Table 6-1.

[redacted]

6.6.3 Pharmacokinetics

At all study sites, blood samples will be collected for PK at the scheduled visits as indicated in Table 6-1.

For a detailed description of the blood sampling schema, including time points, refer to the Blood Collection Log in Appendix 2, Table-14.1.

Blood samples (approximately 2 mL, not less than 1.5 mL) will be collected into Serum Separator Tubes (SST). All blood samples will be taken by direct venipuncture. The blood sample will be allowed to clot over a minimum of 30 minutes at room temperature prior to harvesting of the serum. The serum will be obtained by centrifugation at approx. 2,500 Revolutions Per Minutes (RPM) for 10 minutes.

Thereafter, the serum samples will be placed on ice, split into 2 aliquots (labelled plain barrier polypropylene tubes) and then stored (within 30 minutes of serum collection by centrifugation) at -70˚C to -20˚C. The shipment to the central laboratory should be made on dry ice. The shipment instructions will be provided by the central laboratory. If possible, each aliquot of a sample should be sent separately to the central laboratory. The back-up samples should remain at the central laboratory whereas the second batch (the second pair) is delivered to an analytical laboratory. Back-up samples at the central laboratory will only be disposed after approval by

the corresponding Study Leader (typically six to 12 months after the clinical study report is published).

The actual sample collection date and exact time of collection should be entered in the blood collection for PK eCRF or in the Unscheduled blood collection for PK eCRF, as appropriate. Sampling problems should be noted in the 'Reason sample not taken' section of the eCRF.

6.6.3.1 PK sample handling, labeling and shipment instructions

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

Tubes and labels will be provided by the central laboratory with study/sample type and sample number pre-printed on the label.

6.6.3.2 PK sample stability

Secukinumab is stable in serum samples for **4 months** at -20°C or at -80°C. Long-term data confirmed a stability of 39 months at -65°C to -90°C.

6.6.3.3 PK analytical methods

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

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject ***after providing written informed consent*** for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by

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

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

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

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

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

- The severity grade:
  - Mild: usually transient in nature and generally not interfering with normal activities
  - Moderate: sufficiently discomforting to interfere with normal activities
  - Severe: prevents normal activities
- Its relationship to the study treatment (suspected: no/yes)
- Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- Whether it constitutes a serious adverse event (SAE - Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- Action taken regarding study treatment

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

- No action taken (e.g. further observation only)
- Study treatment dosage increased/reduced
- Study treatment interrupted/withdrawn
- Concomitant medication or non-drug therapy given
- Subject hospitalized/subject's hospitalization prolonged (Section 7.2 for definition of SAE)
- Its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

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

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

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

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

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

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (Annex IV, ICH-E2D Guideline).

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

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

7.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 12 weeks following the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 12 weeks period following the last administration of study treatment should only be reported to Novartis if the investigator suspects a causal relationship to study treatment. Any SAEs reported up to the subject's last visit will be reported in the AE eCRF. SAEs beyond that date will only be recorded in the Novartis Drug Safety and Epidemiology database.

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

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all

investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

Not applicable.

7.4 Renal safety monitoring

Not applicable.

7.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

7.6 Pregnancy reporting

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

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

Any SAE experienced during pregnancy and unrelated to the 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, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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

8.2 Data collection

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

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed

or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

8.3 Database management and quality control

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

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

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

ECG readings will be reviewed locally.

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

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

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

8.4 Data Monitoring Committee

Not planned.

8.5 Adjudication Committee

Not planned.

9 Data analysis

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

Treatment groups for analyses will include:

- Week 12: secukinumab 300 mg (two 1 mL injections of 150 mg s.c.), secukinumab 300 mg (one 2 mL s.c. injection), and placebo
- Week 12 up to Week 52 (end of study): secukinumab 300 mg (two 1 mL injections of 150 mg s.c.), secukinumab 300 mg (one 2 mL s.c. injection), placebo-secukinumab 300 mg (two 1 mL injections of 150 mg) and placebo-secukinumab 300 mg (one 2 mL s.c. injection)
- Entire study: secukinumab 300 mg (two 1 mL injections of 150 mg s.c.), secukinumab 300 mg (one 2 mL s.c. injection), placebo, any secukinumab 300 mg (two 1 mL injections 150 mg s.c.), any secukinumab 300 mg (one 2 mL s.c. injection)

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

9.1 Analysis sets

The following analysis sets will be used in this study:

Randomized set: The randomized set will be defined as all subjects who were randomized. Unless otherwise specified, mis-randomized subjects (mis-randomized in IRT) will be excluded from the randomized set. (mis-randomized subjects are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and double-blind medication was not administered to the subject).

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

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

9.2 Subject demographics and other baseline characteristics

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

9.2.1 Demographics and baseline characteristics

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

percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects.

9.2.2 Medical history

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

9.3 Treatments

9.3.1 Study treatment

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

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

Duration of exposure of a treatment will be defined as the time from first dose of the treatment to the time of treatment switch (for subjects who switch treatment) or minimum of (last dose of the treatment + 84 days) and (last visit date).

9.3.2 Prior and concomitant medication

Prior and concomitant medications will be summarized by treatment group for the different epochs in separate tables.

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the last day of study visit will be a concomitant 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 subjects receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Psoriasis specific pre-study treatments, number of pre-study systemic and biologic psoriasis therapies as well as reason for discontinuation will be presented.

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

9.4 Analysis of the primary variable(s)

Details of the testing strategy including primary endpoints are provided in Section 9.4.2.

9.4.1 Co-primary Variable(s)

The co-primary efficacy variables are PASI 75 response at Week 12 and IGA mod 2011 0 or 1 response at Week 12. The analysis of the co-primary variables will be based on the full analyses set (FAS).

9.4.2 Statistical model, hypothesis, and method of analysis

9.4.2.1 Primary endpoint (co-primary endpoints)

The co-primary endpoints of this study are PASI 75 response and IGA mod 2011 0 or 1 response at Week 12.

The statistical hypotheses are that secukinumab 300 mg (2 mL s.c. injection) is not superior to placebo with respect to the proportion of subjects with PASI 75 response and IGA mod 2011 0 or 1 response at Week 12.

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

- 0 corresponds to placebo
- 1 corresponds to secukinumab 300 mg (2 mL s.c. injection)

The following hypotheses will be tested:

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

In other words:

H_1: Secukinumab 300 mg (2 mL s.c. injection) is not superior to placebo with respect to PASI 75 response at Week 12

H_2: Secukinumab 300 mg (2 mL s.c. injection) is not superior to placebo with respect to IGA mod 2011 0 or 1 response at Week 12

The primary analysis method will be the exact logistic regression with treatment group; baseline bodyweight and baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons of secukinumab dose regimen versus placebo in a pairwise fashion utilizing the logistic regression model fitted. In case of response rates of 0% or of 100% in one of the treatment groups, Fisher's exact test will be applied. Confidence intervals for risk difference will be derived based on the exact method.

The hypotheses H_1 and H_2 will both be tested at level 2.5% (one-sided), and significant results will only be achieved if both tests are rejected. If only one hypothesis is rejected and the other hypothesis is not rejected, superiority of secukinumab 300 mg (2 mL s.c. injection) has not been demonstrated.

9.4.3 Handling of missing values/censoring/discontinuations

The following imputation methods will apply to the missing data:

- Response variables based on PASI score and IGA mod 2011 categories will be imputed with multiple imputations (MI) method as primary imputation method. Multiple imputation (MI) is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Within this analysis the PASI score or IGA mod 2011 categories will be imputed and response variables will be derived based on the imputed scores. In the multiple imputation analysis the response status will be imputed based on the individual treatment arm information.
- Non-responder imputation will be used as sensitivity method: Missing values with respect to response variables based on PASI score and IGA mod 2011 categories will be imputed with non-response regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues), exceptions will apply to the following:
  - If a subject who was responder at visit x-1 and visit x+1 but has missing data at visit x, then the subject will be imputed for visit x.
  - If a subject dropped out of the study prior to last scheduled visit and being responders consecutively at least for two preceding visits, the subject will be imputed as responder for the last scheduled visit.

9.4.4 Sensitivity analyses

Sensitivity analyses will be performed as follows:

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

9.5 Analysis of key secondary variables

9.5.1 Efficacy variables

9.5.1.1 The key secondary endpoints of this study are planned as follows:

- PASI 90 response at Week 12
- PASI 100 response at Week 12

9.5.1.2 Testing strategy

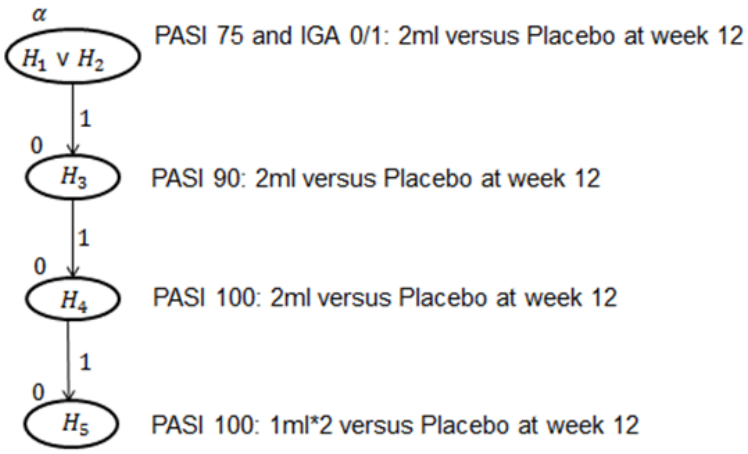
The following hypotheses will be tested sequentially and are included in the hierarchical testing strategy and type-I-errors will be set such that a family-wise type-I-error of 2.5% (one-sided) is kept:

- H_1: secukinumab 300 mg (2 mL s.c. injection) is not superior to placebo with respect to PASI 75 response at Week 12
- H_2: secukinumab 300 mg (2 mL s.c. injection) is not superior to placebo with respect to IGA mod 2011 0 or 1 response at Week 12
- H_3: secukinumab 300 mg (2 mL s.c. injection) is not superior to placebo with respect to PASI 90 response at Week 12

- H_4: secukinumab 300 mg (2 mL s.c. injection) is not superior to placebo with respect to PASI 100 response at Week 12
- H_5: secukinumab 300 mg (two 1 mL s.c. injections of 150 mg secukinumab) is not superior to placebo with respect to PASI 100 response at Week 12

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

Figure 9-1 Testing strategy



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

The testing sequence will continue to H_3 at α (one-sided) only if both H_1 and H_2 have been rejected at α (one-sided). Similarly, the testing sequence will continue to H_4 at α (one-sided) only if H_3 testing has been rejected. In case, H_4 has been rejected at α (one-sided), the corresponding alpha (α) will be passed to the next hypothesis corresponding to H_5.

9.6 Analysis of other secondary and exploratory variables

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

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

For PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response at each visit, pairwise comparison between each secukinumab dose regimen and placebo will be conducted using exact logistic regression model with treatment group, body weight stratum, and baseline PASI as effects.

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

9.6.2 PASI score over time

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

9.6.3 IGA mod 2011 score over time

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

[redacted]

9.6.6 Safety variables

All safety evaluations will be performed on the safety set.

Analysis of adverse events will be based on treatment emergent events, which are defined as events started after the first dose of study treatment and within 84 days after the last study treatment, or events present prior to the first dose of study treatment but increased in severity based on preferred term within 84 days after the last study treatment.

Other safety variables will be based on on-treatment events, which are defined as any events that happened after first dose of study treatment and on or before last dose + 84 days.

9.6.6.1 Adverse events

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

Tabulated summaries will be presented for Treatment Epoch I and all epochs put together.

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

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

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

Exposure adjusted analyses in terms of incidence rate will be provided combining all the study epochs.

9.6.6.2 Laboratory data

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

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

Shift tables with respect to Common Toxicity Grade Criteria (CTCG) and normal ranges will be provided. These summaries will be presented by laboratory test and treatment group. Shifts will be presented for most extreme values post-baseline.

Incidence rates of notable abnormalities will be presented (Appendix 1).

[redacted]

9.6.6.4 Vital signs

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

All information collected will be listed by subject and abnormal values will be flagged (Appendix 1).

9.6.7 Health-related Quality of Life

9.6.7.1 Dermatology Life Quality Index (DLQI)

Summaries will be based on the FAS and will be presented separately for each treatment group.

For each of the seven scores the percentage change from baseline will be derived. Summary statistics will be provided for absolute values as well as for the percentage change by visit and treatment group.

The absolute value and the percentage change from baseline of DLQI total score will be analyzed with the Van-Elteren test using type-II weights, for between-treatment comparison of

the two secukinumab treatment groups versus placebo. The Van-Elteren test will be performed at each visit. Language of the questionnaire and geographical region will be the strata adjusted for in the Van-Elteren test. In addition, stratified Hodges-Lehmann estimates for the median as well as confidence intervals will be derived for the absolute values and percentage change to baseline for each treatment group as well as for treatment comparison between two secukinumab treatment groups versus placebo.

It is understood that conclusions obtained from the confidence intervals of these estimates (mean or Hodges-Lehmann estimates for the median) will not be completely consistent with the testing results (Van-Elteren test) which constitute the key analysis for drawing conclusions.

In addition, summary statistics will be provided for number of subjects achieving DLQI 0 or 1. Treatment groups will be compared by means of Fisher's exact test.

[redacted]

9.6.8 Patient Reported Outcomes (PRO)

9.6.8.1 Subject satisfaction assessment of Self-Injection Questionnaire (SIAQ)

Summary statistics for the domain scores as well as item scores will be provided by visit and treatment group.

Item and domain scores from the PRE module taken before the first self-injection at Randomization will be compared with the corresponding item and domain scores (Feelin about injections, Self-confidence domains and overall satisfaction of self-injection item) from the POST module taken after the two self-injections. Change in domain scores from PRE module will be summarized by visit and treatment group.

[redacted]

9.6.10 Pharmacokinetics

All completed subjects with quantifiable pharmacokinetic (PK) measurements of secukinumab will be included in the pharmacokinetic data analysis. Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. PK concentrations will be summarized by visit and treatment group. In addition to mean, standard deviation, coefficient of variation, median and quartiles, the geometric mean and geometric coefficient of variation and n(log) will be presented.

[redacted]

[redacted]

9.6.13 Pharmacokinetics

Exploratory analysis to investigate the relationship between the PK data and efficacy outcomes will be performed.

[redacted]

9.8 Sample size calculation

A response rate of 8% for PASI 75 response and IGA mod 2011 0 or 1 response in the placebo group is expected, whereas a response rate of 62% for PASI 75 response and 55% for IGA mod 2011 0 or 1 is the anticipated response in the secukinumab 300 mg 2 mL pre-filled syringe group.

Placebo-response rates between 3% and 7% have been reported in Papp et al 2005, Menter et al 2008, Leonardi et al 2008, and Papp et al 2008.

9.8.1 Primary endpoint (co-primary endpoint):

With respect to the co-primary endpoint (PASI 75 response and IGA mod 2011 0 or 1 response at Week 12), the type-I-error will be 2.5% one-sided for comparison. With 70 subjects per group and assuming a response rate of 10% for PASI 75 response and IGA mod 2011 0 or 1 response in the placebo group, the power to show a response rate of 62% for PASI 75 response and 55% for IGA mod 2011 0 or 1 response in the secukinumab 300 mg 2 mL pre-filled group based on Fisher's exact test (nQuery Advisor 6.01, two group Fisher's-exact test of equal proportions) is above 99% for PASI 75 response and IGA mod 2011 0 or 1 response.

9.8.2 Secondary endpoints(s):

A power of 90% to show a response rate of 30% for PASI 100 in the secukinumab 300 mg 2 mL pre-filled group and 8% in the placebo group based on Fisher's exact test results in a sample size of 70 subjects per group. Same power can be achieved if we apply the same assumption of PASI 100 response rate for secukinumab 300 mg 1 mL pre-filled group.

A power of above 99% to show a response rate of 46% for PASI 90 in the secukinumab 300 mg 2 mL pre-filled group and 8% in the placebo group based on Fisher's exact test results in a sample size of 70 subjects per group.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

Novartis will provide to investigators in a separate document a proposed Informed Consent Form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed Informed 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.

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

11 Protocol adherence

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

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

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation, where required. Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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13 Appendix 1: Clinically notable laboratory values and vital signs

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

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

Liver Function and Related Variables

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

Renal Function

Creatinine (serum):	> 1.5 x ULN

Hematology Variables

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

Urinalysis Variable

Protein urine dipstick:	++*

* ++ is ≥ 100 mg/dL

14 Appendix 2: Blood collection log for pharmacokinetics [redacted]

Table 14-1 Blood collection log for pharmacokinetics

Visit/Week	Timepoint	Volume	Analysis	Sample number***	PK collection number /Dose Reference ID
Randomization	Pre-dose	2 mL	AIN457 for PK	1	1
Week 4	Pre-dose	2 mL	AIN457 for PK	2	2
Week 12/EOTEI	Pre-dose	2 mL	AIN457 for PK	3	3
Week 13	168 h (post-dose)*	2 mL	AIN457 for PK	4	3
Week 14	336 h (post-dose)*	2 mL	AIN457 for PK	5	3
Week 15	504 h (post-dose)*	2 mL	AIN457 for PK	6	3
Week 16	672 h (post-dose)*	2 mL	AIN457 for PK	7	3
Week 28	Pre-dose	2 mL	AIN457 for PK	8	4
Week 52/EOTEII	672 hours**	2 mL	AIN457 for PK	9	5

*Post–dose timepoints refer to the dose administered at Week12. PK samples should be drawn before dose/placebo administration at Weeks 13, 14, 15, 16.

**Scheduled post-dose time point for sample number 9 (672 hours post-dose) referred to the last dose given at week 48.

*** If a PK sample is collected at an unscheduled visit, sample numbers will follow the pattern, 1001, 1002, etc.

Note: all blood samples should be taken prior to dosing

[redacted]

15 Appendix 3: Scoring of the SIAQ

The scoring of domains is performed in 2 steps:

1. The raw item scores ranging from 1 to 5 are transformed into scores ranging from 0 (worst experience) to 10 (best experience).
2. The transformed scores for items contributing to a domain are then averaged into a domain score.

Table 15-1 Scoring of domains from raw item scores

	Items	Transformed item score	Domain score calculation	Domain score range
PRE module domain				
FL	1-3	((raw score)-1)*2.5	Average of transformed item scores	0-10
CO	4-6	((raw score)-1)*2.5		
SA	7	((raw score)-1)*2.5		
POST module domain				
FL	1-3	((raw score)-1)*2.5	Average of transformed item scores	0-10
IM	4	((raw score)-1)*2.5		
CO	5-7	((raw score)-1)*2.5		
RE	8-9	((raw score)-1)*2.5		
EU	10-14	**((raw score)-1)*2**		
SA	15-21	((raw score)-1)*2.5		

16 Appendix 4: SIAQ Questionnaire

- Representative example –

PRE-Self-Injection

INTRODUCTION

The following questions ask about injections in general and your feelings about giving yourself an injection.

Thank you for completing this questionnaire by yourself, preferably in a quiet environment. Take as much time as you need to complete it. There are no right or wrong answers. Your answers will remain strictly confidential and anonymous.

Please answer each question below by checking the box that best represents your opinion (Check only one box per question).

1. In general, how afraid are you of needles?

Not at all	A little	Moderately	Very	Extremely
☐5	☐4	☐3	☐2	☐1

2. In general, how afraid are you of having an injection?

Not at all	A little	Moderately	Very	Extremely
☐5	☐4	☐3	☐2	☐1

3. How anxious do you feel about giving **yourself** an injection?

Not at all	A little	Moderately	Very	Extremely
☐5	☐4	☐3	☐2	☐1

SIAQ (Pre-Self-Injection, continued)

4. How confident are you about giving yourself an injection in the right way?

Not at all	A little	Moderately	Very	Extremely
☐1	☐2	☐3	☐4	☐5

5. How confident are you about giving yourself an injection in a clean and sterile way?

Not at all	A little	Moderately	Very	Extremely
☐1	☐2	☐3	☐4	☐5

6. How confident are you about giving yourself an injection safely?

Not at all	A little	Moderately	Very	Extremely
☐1	☐2	☐3	☐4	☐5

7. Overall, how satisfied are you with your current way of taking your medication?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

17 Appendix 5: DLQI Questionnaire

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

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	 Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒

Please check you have answered EVERY question. Thank you.