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Novartis Research and Development

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457A2325 / NCT03589885

Multicenter, rAndomized, double-blind, placebo-conTrolled, 52-week stUdy to demonstRatE the efficacy, safety and tolerability of subcutaneous secukinumab injections with 2 mL auto-injectors (300 mg) in adult subjects with moderate to severe plaque psoriasis – MATURE

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List of abbreviations

AE	Adverse Event
AI	Auto-Injector
ALT/AST	Alanine Aminotransferase/Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
BDR	Bioanalytical Data Report
BSA	Body Surface Area
CD	Cluster of Differentiation
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human use
ClinRO	Clinical Reported Outcomes
CMO & PS	Chief Medical Office and Patient Safety
CRF	Case Report Form
CRO	Contract Research Organization
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End Of Study
EOT1/EOT2	End of Treatment 1/End of Treatment 2
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFU	Instructions For Use
IGA mod 2011	Investigator's Global Assessment modified 2011
IL	Interleukin
IN	Investigator Notification
i.v.	Intravenous(ly)
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRT	Interactive Response Technology
LLN	Local Lab Normal
MedDRA	Medical Dictionary for Regulatory Activities
NIH	National Institutes of Health
PASI	Psoriasis Area and Severity Index
PFS	Pre-Filled Syringe
[redacted]	[redacted]
PRO	Patient Reported Outcome

[redacted]

PsA	Psoriatic Arthritis
SAE	Serious Adverse Event
s.c.	Subcutaneous(ly)
SIAQ	Self-Injection Assessment Questionnaire
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamopyruvate Transferase
SST	Serum Separator Tubes
SUSARs	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TNFα	Tumor Necrosis Factor alpha
UK	United Kingdom
USA	United Sates of America
ULN	Upper Limit of Normal
UV	Ultraviolet
WBC	White Blood Cell
WHO	World Health Organization

[redacted]

Glossary of terms

Control drug	Drug(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (eg, 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (eg, prior to starting any of the procedures described in the protocol)
Period	A portion of the study which serves a specific purpose. Typical periods 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 (Code of Federal Regulations) 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in subjects/subjects with established disease and in those with newly-diagnosed disease.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Study drug/treatment	Any single drug or combination of drugs administered to the subject as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples

[redacted]

Protocol summary

Protocol number	CAIN457A2325
Full Title	Multicenter, rAndomized, double-blind, placebo-conTrolled, 52-week stUdy to demonstRatE the efficacy, safety and tolerability of subcutaneous secukinumab injections with 2 mL auto-injectors (300 mg) in adult subjects with moderate to severe plaque psoriasis - MATURE
Brief title	Study of efficacy and safety of secukinumab 2 mL auto-injector (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 a 2 mL pre-filled auto-injector (AI) of 300 mg secukinumab. Results of this study will support the registration of secukinumab 300 mg 2 mL auto-injector. This 52-week, double-blind, randomized, parallel-group, and placebo-controlled study is using the recommended dose of 300 mg secukinumab which has been approved in Japan, United States of America (USA) , European Union (EU), Switzerland and other countries for the treatment of moderate to severe psoriasis in adults
Primary Objective(s)	The primary objective is to demonstrate the efficacy of secukinumab 300 mg when administered in 2 mL auto-injector in subjects with plaque-type psoriasis with respect to both Psoriasis Area and Severity Index (PASI) 75 and Investigator's Global Assessment modified 2011 (IGA mod 2011) 0 or 1 response (co-primary endpoint) at Week 12, compared to placebo
Secondary Objectives	**Key secondary objective** To demonstrate the efficacy of secukinumab 300 mg when administered with a 2 mL auto-injector in subjects with plaque-type psoriasis with respect to PASI 90 at Week 12, compared to placebo. **Other secondary objectives** • To assess the efficacy of secukinumab 300 mg when administered with a 2 mL auto-injector in subjects with 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 auto-injectors as assessed by vital signs, clinical laboratory variables, and adverse events (AE) monitoring, compared to placebo. • To assess the subject usability (ability to follow instructions for use (IFU) and potential use-related hazards) and satisfaction with the new secukinumab 2 mL auto-injectors utilizing a self-administered Self-Injection Assessment Questionnaire (SIAQ) and investigator/site staff observation of secukinumab 300 mg 2 mL auto-injector administration.

	• To investigate the effects of secukinumab 300 mg when administered with a 2 mL auto-injectors 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-week multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in approximately 120 subjects with moderate to severe plaque-type psoriasis. The study consists of 3 periods: Screening Period (of at least 1 week and up to 4 weeks), Treatment Period 1 (12 weeks) and Treatment Period 2 (40 weeks). Subjects will be randomized using a 2:2:1:1 ratio to the following groups following a stratification by body weight (< 90 .kg or ≥ 90 kg): secukinumab 300 mg regimen group (2 mL auto-injector), secukinumab 300 mg regimen group (2 x 1 mL pre-filled syringes (PFS)). Placebo – Secukinumab 300 mg (2 mL AI) or to Placebo – Secukinumab 300 mg (2 x 1mL PFS). The treatment of the 2 placebo groups will be the same during treatment Period 1 and will only differ after Week 12 in treatment period 2 for non-responders only. Prior to administration of the Week 12 dose, PASI 90 response will be evaluated and subjects classified accordingly. Based on the PASI 90 responders at the Week 12 visit, subjects on placebo will either remain on placebo during the Treatment Period 2 or be re-assigned to secukinumab 300 mg treatment (2 mL AI or 2 x 1mL PFS).
Population	Approximately 120 subjects with moderate to severe plaque psoriasis will be randomized in approximately 30 centers worldwide. Approximately 150 subjects are expected to be screened to provide the number of randomized subjects.
Key Inclusion criteria	1. Subjects must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study related activity is performed. Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations. 2. Men or women 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 (eg, 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. Subjects not willing to limit Ultraviolet (UV) light exposure (eg, 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 Interleukin (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 human chorionic gonadotropin (hCG) laboratory test. 7. 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). 8. 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 as one 2 mL auto-injector Control Treatment: • Secukinumab 300 mg, provided as two 1 mL pre-filled syringes (containing 150 mg secukinumab each) • Secukinumab placebo, provided as one 2 mL auto-injector and two 1 mL pre-filled syringes containing placebo matching secukinumab
Efficacy assessments	• IGA mod 2011 • PASI

[redacted]

[redacted]	[redacted]
Key safety assessments	• Evaluation of all AEs and Serious AEs (SAEs) • Physical examination • Vital signs • Height and weight • Laboratory evaluations (including hematology, clinical chemistry, fasting laboratory evaluations, urinalysis) [redacted] • ECG • Pregnancy
[redacted]	• Usability and hazard assessment of the auto-injector • Self-Injection Assessment Questionnaire (SIAQ) • Dermatology Life Quality Index (DLQI) • [redacted]
Data analysis	Treatment groups for analyses will include: Primary week 12 analysis: • secukinumab 300 mg 2 mL Auto-injector (AI), secukinumab 150 mg 1 mL Pre-Filled Syringe (PFS) x 2, and placebo • Entire study: secukinumab 300 mg 2 mL AI, secukinumab 150 mg 1 mL PFS x 2, placebo switched secukinumab 300 mg 2 mL AI, placebo switched secukinumab 150 mg 1 mL PFS x 2, any secukinumab 300 mg 2 mL AI, any secukinumab 150 mg 1 mL PFS x 2, any secukinumab 300 mg and placebo The following hypotheses will be included in co-primary testing procedure: • H1: secukinumab 300 mg (2 mL AI) is not superior to placebo with respect to PASI 75 response at Week 12 • H2: secukinumab 300 mg (2 mL AI) is not superior to placebo with respect to IGA mod 2011 0 or 1 response at Week 12 Within each of hypotheses H1 and H2 is tested at $\alpha = 2.5\%$ (one-sided). The testing sequence will continue to key secondary endpoint PASI 90 at $\alpha = 2.5\%$ (one-sided) only if both H1 and H2 have been rejected at α (one-sided) such that a family-wise type-I-error of α (one-sided) is kept. • H3: secukinumab 300 mg (2mL AI) is not superior to placebo with respect to PASI 90 response at Week 12 The primary analysis method will be the logistic regression with treatment group; baseline bodyweight strata and baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons of secukinumab dose regimen versus placebo utilizing the logistic regression model fitted. In case the logistic regression does not converge, an exact logistic regression will be performed. 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.

[redacted]

	Missing data will be imputed using multiple imputations (MI) method as primary imputation method.
Key words	psoriasis, PASI, IGA mod 2011, secukinumab, auto-injector

[redacted]

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 and Mrowietz 2003, Griffiths and Barker JNWN 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 healthcare 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 (eg, 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 (eg, not achieving a decrease in 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-Interleukin (IL) 12/23 class of biological drugs provided clinicians with another treatment option (Kerdel and Zaiac 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 have been investigated in Phase III studies for the treatment of a range of immune mediated inflammatory diseases (Puig 2014) amongst which ixekizumab and brodalumab have been approved in 2017 in USA for moderate to severe psoriasis patients.

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

[redacted]

and neutralizes the bioactivity of this cytokine. IL-17A is the central cytokine of a newly defined subset of inflammatory T cells, the T helper 17 cells which, in several animal models, are pivotal in multiple autoimmune and inflammatory processes. IL-17A is produced by memory effector CD4+ and CD8+ T lymphocytes, but also largely by innate immune cells (including neutrophils, mast cells, γδ-T cells, ILC3 cells, NK and iNKT cells), 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., IL-17A). Secukinumab (Cosentyx®) with a recommended dose of 300 mg was approved in 2014 in Japan, and 2015 in USA, EU, Switzerland, and in many 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 (AI). 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 pre-filled syringe and the 2 mL auto-injector containing 300 mg of secukinumab.

As of 25 June 2017, over 28 000 subjects have been enrolled in studies with secukinumab, with over 25000 having 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 2017, there are over 50 completed and multiple ongoing trials conducted with secukinumab in indications including psoriasis, psoriatic arthritis (PsA), 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 Novartis 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, [redacted] and local tolerability of a 2 mL auto-injector of 300 mg secukinumab.

1.2 Purpose

The purpose of this study is to demonstrate efficacy of secukinumab 300 mg in 2 mL auto-injector at Week 12 based on PASI and IGA mod 2011 response rates versus placebo in subjects with moderate to severe plaque-type psoriasis.

Moreover this study will assess the efficacy, safety and tolerability of secukinumab when used for 52 weeks as well as usability (ability to follow instruction for use and potential use-related hazards) of the 2 mL AI.

As a result, this study will provide efficacy, [redacted] and safety data ([redacted]) to support the registration of the secukinumab 300 mg in 2 mL AI.

[redacted]

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • To demonstrate the efficacy of secukinumab 300 mg when administered in 2 mL auto-injector 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.	**Endpoint(s) for primary objective(s)** • PASI 75 response at Week 12 and IGA mod 2011 0 or 1 response at Week 12
Key Secondary Objective • To demonstrate the efficacy of secukinumab 300 mg when administered in 2 mL AI in subjects with plaque-type psoriasis with respect to PASI 90 at Week 12, compared to placebo.	**Endpoint for key secondary objective** • PASI 90 response at Week 12
Other Secondary Objective(s)	**Endpoint(s) for other secondary objective(s)**
• To assess the efficacy of secukinumab 300 mg when administered in 2 mL AI in subjects with 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.	• PASI score and IGA mod 2011 score at each visit up to week 52 • PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response at each visit up to week 52
• To investigate the clinical safety and tolerability of secukinumab 300 mg 2 mL AI as assessed by vital signs, clinical laboratory variables, and adverse events monitoring, compared to placebo.	• Treatment emergent adverse events, change from baseline to each study visit in clinical laboratory variables and vital signs
• To assess the subject usability (ability to follow instructions for use and potential use-related hazards) and satisfaction with the new secukinumab 2 mL AI utilizing a self-administered SIAQ and investigator/site staff observation of secukinumab 300 mg 2 mL AI administration.	• Successful self-injection, subject use errors, item and domain scores from the SIAQ, change in SIAQ domain scores
• To investigate the effects of secukinumab 300 mg when administered in 2 mL AI with respect to DLQI 0 or 1 achievement and DLQI changes at Week 12 compared to placebo, and over time up to Week 52.	• DLQI 0 or 1 score at each visit • Change from baseline in each of the seven DLQI scores and in the DLQI total score
[redacted]	
[redacted]	

Objective(s)	Endpoint(s)
[redacted]	

3 Study design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in approximately 120 subjects with moderate to severe plaque-type psoriasis.

It is expected that subjects will be enrolled at around 30 study sites worldwide.

The study consists of 3 periods:

- Screening Period (of at least 1 week and up to 4 weeks between Screening and Randomization)

The screening period is used to assess eligibility of the subjects and to taper subjects off prohibited medications.

- Treatment Period 1 (of 12 weeks, double-blind between Randomization and Week 12 pre-dose)

The Treatment Period 1 starts with the randomization of eligible subjects followed by the first dosing. At the start of Treatment Period I, eligible subjects will be randomized at a 2:2:1:1 ratio to one of the four treatment groups (Section 6.1.1). In order to achieve a balanced weight distribution in each treatment arm, randomization in these four groups will be stratified by body weight at baseline (< 90 kg or ≥ 90 kg). Subjects are then visiting the study site at Week 1, 2, 3, 4, 8 and 12, where they will receive study treatment (secukinumab 300 mg 2 mL AI, secukinumab 300 mg 2 x 1mL PFS, or placebo).

[redacted]

Assessments for the primary endpoints are done for all treatment arms at Week 12 prior to dosing. This time-point is the End of Treatment Period 1 (EOT1).

- Treatment Period 2 (of 40 weeks, double-blind between Week 12 dosing and Week 52)

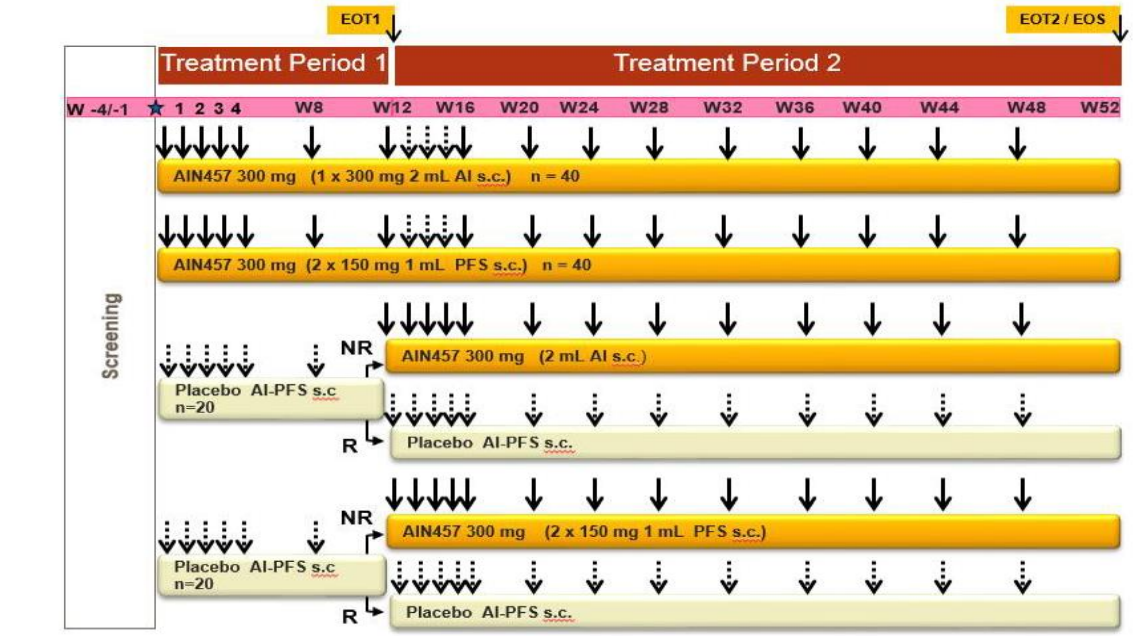
The Treatment Period 2 is a maintenance period for the study treatment and starts with the Week 12 dosing. Doses of study treatment are then self-administered weekly up to Week 16 and every four weeks up to Week 48 for all treatment arms.

Week 52 is the planned End of Treatment Period 2/End of Study (EOT2/EOS).

Subjects who prematurely discontinue study treatment must perform EOT1 or EOT2/EOS approximately four weeks after their last dose of study treatment, depending if they are in Treatment Period 1 or 2, respectively.

Safety, efficacy [redacted] will be performed according to the visit schedule as described in Table 8-1.

Figure 3-1 Study design



★ = Randomization
W = Week
NR = PASI 90 non responder
R = PASI 90 responder

In the figure, the solid arrow means active drug dosing while the dotted arrow means placebo dosing.

4 Rationale

4.1 Rationale for study design

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

[redacted]

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

The study has been designed in accordance with Health Authorities guidelines and feedback on the clinical development program for the 2 mL auto-injector, including the United States Food and Drug Administration (FDA). 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 2016). 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 CAIN457A2325.

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 (1 mL pre-filled syringe in CAIN457A2308, and 1 mL auto-injector in CAIN457A2309; Blauvelt et al 2014, Paul C et al 2015).

Overall, this study will assess the efficacy, [redacted] safety ([redacted]) and tolerability of secukinumab when used both, short-term (up to 12 weeks) and long-term (up to 52 weeks) and includes an usability and satisfaction assessment (ability to follow instruction for use and potential use-related hazards) and satisfaction) of secukinumab with a 2 mL auto-injector. These data will support the registration of secukinumab 300 mg 2 mL auto-injector.

The subject population will be described in more detail in Section 5 below.

4.2 Rationale for dose/regimen and duration of treatment

The placebo-controlled study design was chosen to demonstrate the efficacy of 300 mg secukinumab administered with a 2 mL auto-injector 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 a 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 [redacted] and safety profile with the secukinumab 300 mg 2 mL auto-injector.

4.3 Rationale for choice of comparator

Due to the nature of psoriasis and the outcome measures for the primary and the key secondary endpoints used (PASI 75, 90 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

[redacted]

the indication of plaque-type psoriasis. Subjects from the placebo group that will not achieve PASI 90 after Week 12 will receive secukinumab.

An arm with secukinumab 300 mg as 2 injections of 1 mL PFS has been added to assess [redacted] and as a reference for comparisons of efficacy and safety with secukinumab 300 mg 2 mL AI.

4.4 Purpose and timing of interim analyses/design adaptations

An analysis is planned to be performed after all subjects have completed the Week 16 visit to assess the [redacted] data up to Week 16 with the coprimary endpoints.

All data up to Week 16 will be collected with the clinical team being blinded. The designated Novartis personnel (eg, statistician, programmer and a clinical representative) will be unblinded following database lock for the Week 16 analysis after all subjects have completed Week 16. Investigators, site personnel, and subjects will remain blinded until the end of the study.

It is planned that data from the Week 16 analysis will be used for submission to the Health Authorities. Trial modifications are not planned based on any Week 16 analysis.

Additional analyses are not planned, they may be performed to support Health Authorities interactions, as necessary.

4.5 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.

Approximately 4,000 patients with moderate to severe plaque psoriasis were included in studies in the registration program. This included 3,430 subjects 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 [redacted] 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.

[redacted]

Indirect comparisons across phase III trials revealed that 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 subjects with a simple easy to use single-injection device for the treatment of psoriasis.

The principle of a 2 mL s.c. injection in patients is supported by the Patient Education document from the US National Institute of Health (NIH) that outlines the possibility to administer more than 1 mL of volume (NIH 2016).

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 auto-injector, and therefore it is appropriate to initiate study CAIN457A2325 for registration purposes.

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

Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

5 Population

Approximately 120 subjects with moderate to severe plaque psoriasis will be randomized in approximately 30 centers worldwide. Approximately 150 subjects are expected to be screened to provide the number of randomized subjects. Drop-outs after randomization will not be replaced.

[redacted]

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet 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

5.2 Exclusion criteria

Subjects meeting 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 (eg, 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. Subjects not willing to limit Ultraviolet (UV) light exposure (eg, 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.

[redacted]

6. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
7. Women of 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 (eg, 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 (eg, 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). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
   - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository.
   - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device or intrauterine system.

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

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the Informed Consent Form (ICF).

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

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

[redacted]

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 (repeated values of systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 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 (TB) infection as defined by a positive central laboratory test result at screening. Subjects with a positive test result may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local country guidelines prior to randomization.
12. Past medical history record or current infection with Human Immunodeficiency Virus, 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 (eg, because of poor tolerability or lack of access to veins) or to self-administer sub-cutaneous injections.
15. History or evidence of ongoing alcohol or drug abuse, within the last six months before Randomization.
16. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

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

Investigational treatment:

- Secukinumab 300 mg, provided as one 2 mL auto-injector (AI)

[redacted]

Control treatment:

- Secukinumab 300 mg, provided as two 1 mL pre-filled syringes (PFS) containing 150 mg secukinumab
- Secukinumab placebo, provided as either one 2 mL AI or two 1 mL PFS

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.

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

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

Subjects will be randomized using a 2:2:1:1 ratio into one of the following 4 treatment arms.

In order to achieve a balanced weight distribution in each treatment arm, randomization will be stratified by body weight at baseline, < 90 kg or ≥ 90 kg.

- Group 1: Secukinumab 300 mg (2 mL AI)
- Group 2: Secukinumab 300 mg (2 x 1 mL PFS)
- Group 3: Placebo - Secukinumab 300 mg (2 mL AI)
- Group 4: Placebo - Secukinumab 300 mg (2 x 1 mL PFS)

During Treatment Period 1, subjects will self-administer three injections of study treatment at study sites (Table 8-1) once weekly at Randomization, Weeks 1, 2, and 3, followed by dosing at Week 4 and Week 8:

- Group 1: one 2 mL secukinumab 300 mg AI plus two 1 mL PFS matching placebo secukinumab s.c. injections
- Group 2: two 1 mL secukinumab 150 mg PFS plus one 2 mL AI matching placebo secukinumab s.c. injections
- Group 3 and Group 4: will receive placebo treatment administered as two 1 mL placebo secukinumab 150 mg PFS plus one 2 mL AI matching placebo secukinumab s.c. injections

The treatment of the 2 placebo groups will be the same during treatment Period 1 and will only differ after Week 12 in treatment period 2 for non-responders only.

Prior to administration of the Week 12 dose, PASI 90 response status will be evaluated and subjects classified accordingly. Based on the PASI 90 responders status (per definition in Section 8.3.2) at the Week 12 visit, subjects on placebo will either remain on placebo during the Treatment Period 2 or be re-assigned to secukinumab 300 mg treatment.

The 2 placebo groups will be considered as a single placebo arm for analysis purpose (up to Week 12).

[redacted]

During Treatment Period 2, subjects will self-administer three injections of study treatment at study sites or at home (Table 8-1) every four weeks starting at Week 12 up to Week 48:

- Group 1: one 2 mL secukinumab 300 mg AI plus two 1 mL PFS matching placebo secukinumab s.c. injections
- Group 2: two 1 mL secukinumab 150 mg PFS plus one 2 mL AI matching placebo secukinumab s.c. injections
- Group 3 and Group 4 (on placebo during Treatment Period 1):
  1. PASI 90 non-responders of Group 3: one 2 mL secukinumab 300 mg AI plus two 1 mL PFS matching placebo secukinumab s.c. injections
  2. PASI 90 non-responders of Group 4: two 1 mL secukinumab 150 mg PFS plus one 2 mL AI matching placebo secukinumab s.c. injections
  3. PASI 90 responders of Group 3 and Group 4: will continue to receive the same placebo treatment administered as two 1 mL placebo secukinumab 150 mg PFS plus one 2 mL AI matching placebo secukinumab s.c. injections.

In addition, subjects will self-administer three injections of study treatment at study sites (Table 8-1) once weekly at Weeks 13, 14 and 15:

- PASI 90 non-responders of placebo Group 3: one 2 mL secukinumab 300 mg AI plus two 1 mL PFS matching placebo secukinumab s.c. injections
- PASI 90 non-responders of Placebo Group 4: two 1 mL secukinumab 150 mg PFS plus one 2 mL AI matching placebo secukinumab s.c. injections
- Group 1, Group 2 and PASI 90 responders of Placebo Group 3 and Group 4: two 1 mL placebo secukinumab 150 mg PFS plus one 2 mL AI matching placebo secukinumab s.c. injections.

6.1.4 Treatment duration

The planned duration of treatment is 52 weeks. Subjects may be discontinued from treatment earlier at the discretion of the investigator or the subject

6.2 Other treatment(s)

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

6.2.1 Concomitant therapy

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 on the appropriate Case Report Forms.

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 appropriate Case Report Forms and should be avoided

during the 12 hours preceding a scheduled visit. Use of any other non-medicated interventions should be recorded on the appropriate Case Report Forms.

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

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

6.2.2 Prohibited medication

Use of any treatments displayed in Table 6-1 that could confound the efficacy of the investigational drug is **NOT** allowed during the study for any indication. All prohibited treatments should be washed out as shown in Table 6-1.

The investigator should instruct the subject to notify the study site about any new treatments. At the discretion of the investigator, if any use of a prohibited treatment presents an undue safety risk for the subject, the study treatment must be discontinued. If a live vaccination has to be administered, the study treatment must be discontinued.

Table 6-1 Prohibited medication

Prohibited treatments[1, 2]	**Washout period (before randomization)**	**Note** [1] If a prohibited treatment of psoriasis is used during the study, the subject should discontinue use of the prohibited treatment if he/she wishes to continue in the study. [2] In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator.
Alefacept, briakinumab, efalizumab, ustekinumab	24 weeks	
Etanercept	4 weeks	
Biological immunomodulating agents other than above (eg, adalimumab, infliximab)	12 weeks	
Other systemic immunomodulating treatments (eg, Methotrexate, cyclosporine A, corticosteroids, cyclophosphamide)	4 weeks	
Other systemic psoriasis treatments (eg, retinoids, fumarates, apremilast)	4 weeks	
Photochemotherapy (eg, psoralen and ultraviolet A (PUVA))	4 weeks	
Phototherapy (e.g., UVA, UVB)	2 weeks	

[redacted]

Prohibited treatments[1, 2]	Washout period (before randomization)	Note
		[1] If a prohibited treatment of psoriasis is used during the study, the subject should discontinue use of the prohibited treatment if he/she wishes to continue in the study. [2] In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator.
Topical treatment[3,4,5] that is likely to impact signs and symptoms of psoriasis (eg, corticosteroids [CS], vitamin D analogues, pimecrolimus, tacrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tar, urea, α-hydroxy or fruit acids)	2 weeks	[3] Including intra-articular or peri-articular injections. Note that inhaled corticosteroids as well as corticosteroid drops in the eye or ear or nasal sprays are permitted. [4] Mild to moderate topical corticosteroids are allowed only during the screening period if used only on the face, scalp, hands and feet and/or genitoanal area and if not used during the 12 h preceding the randomization visit. [5] Topical corticosteroids and other topical treatments will be allowed during treatment period 2 only if (all must apply): •medication is started after the Week 12 visit was completed; •medication is used for 14 consecutive calendar days or less; •medication is used for an indication other than psoriasis and not on the area affected with psoriasis.
Live vaccinations[6]	6 weeks	[6] If the subject received a live vaccination during the study, the subject must discontinue study treatment.
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)	

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

UVA and UVB: Ultra Violet rays A and B

Exposure to light

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

6.2.3 Rescue medication

Use of rescue medication is not permitted in this study

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database.

[redacted]

Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

If a subject is re-screened for the study, then he/she must sign a new ICF and be issued a new Subject Number prior to any assessment being conducted for the subject under the new Subject Number

6.3.2 Treatment assignment, randomization

At Randomization visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. No re-randomization will be done at Week 12 as the original randomization is already including the Period 2 treatment group to be assigned to for Non-responders of the placebo arm. 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 one 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 subject.

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 Global Clinical Supplies 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 should be recorded on the appropriate Case Report Forms.

Randomization will be stratified by body weight assessed at baseline. Stratification ensures a balanced allocation of subjects to treatment groups within the two weight strata: “body weight < 90 kg” or “body weight ≥ 90 kg”.

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

6.4 Treatment blinding

A double-dummy design is used to ensure that the identity of the study drug cannot be disguised, as the drug products are visibly different.

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

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:

- Specific vendors whose role in trial conduct requires their unblinding (eg, IRT)
- Global Clinical Supplies

[redacted]

• The designated Novartis study team members involved in the primary endpoint analysis, as described in Section 4.4.

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

Unblinding will only occur in the case of subject emergencies, at the time of the endpoint analysis as described below. The blind will be kept until the final database lock.

[redacted]

The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason. Study treatment must be discontinued after emergency unblinding (Section 6.6.2).

6.5 Dose escalation and dose modification

Study treatment dose adjustments and/or interruptions are not permitted. However a positive urine pregnancy test during the study requires immediate interruption of study treatment until serum pregnancy test is performed and found to be negative. If the serum test is positive, study treatment must be permanently discontinued.

6.5.1 Follow-up for toxicities

Not applicable.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

All doses of study treatment administration will be recorded on the appropriate case report form. 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 and empty medication boxes/outer packing/devices should be collected (as permitted by local regulations) for compliance checks by field monitors.

6.6.2 Emergency breaking of assigned treatment code

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

[redacted]

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)
- subject number

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

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 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 designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO 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. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

The subjects will record the date(s) of administration at home on a diary/form and will return the used medication and packaging at their next visit to the site. Subjects will be asked to return all unused medication and packaging the latest at the completion of the study or at the time of

[redacted]

discontinuation of the investigational treatment. Site staff will record in the appropriate documents the dates of the administration. Detailed instructions will be provided separately.

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

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

All doses of study treatment (secukinumab and/or placebo) will be self-administered by the subject either at the study site or at home.

The first use at Randomization and the Visit 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 by the site staff walking them through the Instructions For Use (IFU) on how to self-inject via the PFS and AI (the 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 and auto-injector). At Randomization and Week 1, site staff will observe and complete the self-injection assessment checklist (Table 8-5) and the possible hazard assessment check list (Table 8-6) for the 2 mL auto-injector.

Home administrations should be done at pre-defined visits (Table 8-1) and can be performed by the subject. If self-administration is not chosen, these administrations can be performed by a 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 site 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

All doses of study treatment that are administered at the study site should be performed after the study assessments for the visit, including blood sampling and the completion of DLQI questionnaire by the subjects, have been completed.

The first study treatment administration will occur at the Randomization/baseline Visit, after all study scheduled assessments have been performed (and inclusion/exclusion criteria confirmed) and only after the scheduled blood samples have been drawn.

[redacted]

The study treatment solutions must be self-injected subcutaneously in **non-affected** areas of the skin starting with the 2 mL AI, the 2 injections of 1 mL PFS taking place subsequently, after completion of the SIAQ, when applicable. Administration of study treatment may vary on the body regions, i.e., changing the injection site from visit to visit: right thigh, left thigh, right stomach, left stomach, upper outer arm (when assisted by attendant), whilst separating the 2 mL AI and the two 1 mL PFS injection sites. Used syringes and AI should be disposed immediately after use in a sharps container or according to the regulatory needs of the respective countries. More information can be found in the study-specific IFU.

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

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

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

7 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.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), 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 agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (eg, 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

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 investigational drug 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 then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

[redacted]

Subjects might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

8 Visit schedule and assessments

Assessment schedule lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits as outlined in the assessment schedule or as close to the designated day/time as possible. Every effort should be made to respect the timeframe for all visits and particularly when [redacted]. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for the final visit as soon as possible at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse events and concomitant medications recorded on the CRF.

For subjects who discontinue study treatment prematurely for any reason other than withdrawal of informed consent or loss to follow-up procedures as described in Section 9 should be followed.

During Treatment Periods 1 and 2, subjects may be seen at an unscheduled visit, eg, 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 8-1 is as follows (may vary depending on different type of visits):

Investigator / Qualified Site Staff

1. IGA mod 2011
2. PASI
3. Other procedures
   - All remaining study visit procedures (eg, laboratory and [redacted] 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 EOT1 Visit Week 12.
   - Contact IRT to register the subject visit.
   - Prepare the corresponding study medication packs as indicated in the study-specific IFU brochure (dispense for home administrations, as required).
   - Provide guidance to subjects for self-administration prior to the first treatment administration (Section 6.7.2) at Randomization; from Visit Week 1 until End of Treatment Period 2 subjects should refer to the IFU and proceed with self-

[redacted]

administrations either at the site or they receive instructions for sub-sequent home administrations.

- Auto-injector usability and hazard assessment should be done by site personnel, at Randomization Visit and at Visit Week 1 while the injections with the 2 mL AI are self-administered by the subject prior to the 1 mL PFS injection.

Subjects

- Subjects must complete the DLQI prior to any investigator assessments.
- SIAQ PRE module must be completed once at Randomization prior to the first injection with the 2 mL AI.
- SIAQ POST module, must be completed after the injections with the 2 mL AI as shown in Table 8-1.

  The 1 mL PFS injection should follow the SIAQ POST.

[redacted]

Table 8-1 Assessment schedule

Period	**Screening**	**Treatment Period 1**						**Treatment Period 2**															U
Week (relative to Randomization)	**≤ -4**	**R[g]**	**1**	**2**	**3**	**4**	**8**	**12[a] EOT1**	**13**	**14**	**15**	**16**	**20[i]**	**24[i]**	**28**	**32[i]**	**36[i]**	**40**	**44[i]**	**48[i]**	**52[b] EOT2/ EOS**	
Day	**≥ -28 to ≤ -7**	**R**	**8**	**15**	**22**	**29**	**57**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	
Obtain informed consent*	X																					
Demographics	X																					
Inclusion/exclusion criteria[c]	S	S																				
Smoking history	X																					
Psoriasis medical history	X																					
Previous psoriasis therapies	X																					
Cardiovascular medical history	X																					
Other medical history	X																					
Prior or Concomitant non-drug therapies/procedures	Update as necessary																					
Concomitant medications[h]	Update as necessary																					
Physical Exam[c]	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
Lab analysis: safety panel[d] (Hematology and chemistry)	X	X						X				X			X			X			X	X
Fasting labs: glucose, lipid panel[d]		X																				

[redacted]

Period	**Screening**	**Treatment Period 1**						**Treatment Period 2**														U
Week (relative to Randomization)	**≤ -4**	**R[g]**	**1**	**2**	**3**	**4**	**8**	**12[a] EOT1**	**13**	**14**	**15**	**16**	**20[i]**	**24[i]**	**28**	**32[i]**	**36[i]**	**40**	**44[i]**	**48[i]**	**52[b] EOT2/ EOS**	
Day	**≥ -28 to ≤ -7**	**R**	**8**	**15**	**22**	**29**	**57**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	
Urinalysis (local)	S																					S
Tuberculosis test[d]	X																					X
Serum pregnancy test[d,e]	X																					
Urine pregnancy test (local)[e]		S																			X	X
ECG (standard 12 lead)[c]	S																					
[redacted]																						
PASI	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
DLQI		X						X							X						X	X
SIAQ[f]		X	X			X	X	X							X							
Usability and hazard assessment		X	X																			
AE/SAE assessment[h]	Update as necessary																					
Self-injection of study treatment at site		X	X	X	X	X	X	X	X	X	X	X			X			X				
Self-injection of study treatment at Home[h]													X	X		X	X		X	X		
Randomization by IRT[i]		X																				
Contact IRT for drug assignment[a]		X	X	X	X	X	X	X	X	X	X	X			X			X				X

[redacted]

Period	**Screening**	**Treatment Period 1**						**Treatment Period 2**														U
Week (relative to Randomization)	**≤ -4**	**R[g]**	**1**	**2**	**3**	**4**	**8**	**12[a] EOT1**	**13**	**14**	**15**	**16**	**20[i]**	**24[i]**	**28**	**32[i]**	**36[i]**	**40**	**44[i]**	**48[i]**	**52[b] EOT2/ EOS**	
Day	**≥ -28 to ≤ -7**	**R**	**8**	**15**	**22**	**29**	**57**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	
Disposition (EOT1 /EOT2/EOS completion)	X																					

AE = adverse event, BSA = Body Surface Area, DLQI = Dermatology Life Quality Index, eCRF = electronic case report form, , R = randomization, S = assessment to be recorded in the source documentation only, U = unscheduled visits - assessments performed at unscheduled visits are at investigator's discretion

U = assessment to be recorded in the clinical database or received electronically from a vendor

*Informed consent obtained prior to all study specific screening procedures

[a] During Visit Week 12, subjects will have their last assessments performed for the Treatment Period 1 prior to the dose.

[b] EOT1 or EOT2/EOS must be completed for treatment discontinuations from Treatment Period 1 or 2, respectively.

[c] Data regarding to which inclusion/exclusion criteria are not met are captured on the appropriate eCRF.

[d] Samples will be shipped to and analyzed by the central laboratory. The Tuberculosis test may be repeated if the result is "indeterminate", this is performed during the Screening Period.

[e] 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.

[f] SIAQ PRE module only at Randomization, SIAQ POST module for all SIAQ time points after 2 mL AI injection

[g] The PASI Score and IGA mod 2011 will be calculated by the PI to confirm the subject eligibility based on IGA mod 2011, PASI and BSA. At Visit Week 12 (EOT1), the site will calculate the PASI 90 responder status. Both will be entered in IRT and in the eCRF.

[h] During home administrations, adverse events that may occur as well as concomitant medication should be collected by the investigator and reported in the eCRF.

[i] Study treatment will be self-administered at home at Weeks 20, 24, 32, 36, 44, and 48, and at study site for all other visits.

[redacted]

8.1 Screening

Screening

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 is re-screened for the study, then the subject must sign a new ICF and be issued a new Subject Number prior to any assessment being conducted for the subject under the new Subject Number. The investigator/qualified site staff will record if the subject was re-screened on the re-screening section of the 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 appropriate eCRF page 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 (including any chest x-ray), if applicable, if performed not more than 12 weeks before randomization.

8.1.1 Information to be collected on screening failures

Subjects who sign the ICF and discontinue prior to randomization at the Randomization Visit are considered screening failures. IRT must be notified within five days and the reason for not being randomized will be entered in the appropriate eCRF page. The Screening Visit date, the Demography, Informed Consent, and Inclusion/Exclusion Criteria eCRF sections should be completed. The Adverse Event eCRF section and a SAE Form should be completed for any SAE that occurred during the Screening Period. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. The Withdrawal of consent eCRF section should be completed if consent was withdrawn prior to the randomization.

8.2 Subject demographics/other baseline characteristics

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF

8.2.1 Demographics

Subject demographic data will include: age (in years), sex, race, ethnicity, and child-bearing potential (for females only).

8.2.2 Psoriasis medical history/previous psoriasis therapies

The following information should be collected and entered in the eCRF section 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, eg:
  - Generalized pustular or pustular palmoplantar psoriasis
  - Guttate, palmoplantar, nail, inverse, scalp or erythrodermic psoriasis

[redacted]

- 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

8.2.3 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.

8.2.4 Cardiovascular medical history

Any information pertaining to cardiovascular medical history assessed prior to randomization should be recorded on the appropriate case report form.

8.2.5 Medical history

Relevant medical history and current medical conditions present before signing the informed consent should be recorded on the appropriate eCRF section. 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 sections, see above.

8.2.6 Determination of the tuberculosis status

Determination of the 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. Any significant findings should be recorded on the appropriate eCRF page (Tuberculosis assessment or medical history as deemed necessary) (See Appendix 6 for more details).

8.3 Efficacy

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

- IGA mod 2011
- PASI

8.3.1 Investigator's Global Assessment (IGA mod 2011)

It is recommended that the same evaluator conduct the assessment throughout the study whenever possible.

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.

[redacted]

Table 8-2 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.

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

The investigator or qualified designee will complete the PASI assessment. 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 as first step of PASI calculation from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see Table 8-3). The following calculations will be done: each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added up to estimate the total BSA affected by plaque-type psoriasis.

A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) will be derived as indicated in Table 8-3. 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.

[redacted]

The buttocks are assessed as part of the lower limbs.

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

Table 8-3 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)†	0 = none	0 = none	0 = none	0 = no involvement
	1 = slight	1 = slight	1 = slight	1 = > 0 - < 10
	2 = moderate	2 = moderate	2 = moderate	2 = 10 - < 30
	3 = severe	3 = severe	3 = severe	3 = 30 - < 50
	4 = very severe	4 = very severe	4 = very severe	4 = 50 - < 70
				5 = 70 - < 90
				6 = 90 - 100
Trunk (T)‡	0 = none	0 = none	0 = none	0 = no involvement
	1 = slight	1 = slight	1 = slight	1 = > 0 - < 10
	2 = moderate	2 = moderate	2 = moderate	2 = 10 - < 30
	3 = severe	3 = severe	3 = severe	3 = 30 - < 50
	4 = very severe	4 = very severe	4 = very severe	4 = 50 - < 70
				5 = 70 - < 90
				6 = 90 - 100
Upper limbs (U)	0 = none	0 = none	0 = none	0 = no involvement
	1 = slight	1 = slight	1 = slight	1 = > 0 - < 10
	2 = moderate	2 = moderate	2 = moderate	2 = 10 - < 30
	3 = severe	3 = severe	3 = severe	3 = 30 - < 50
	4 = very severe	4 = very severe	4 = very severe	4 = 50 - < 70
				5 = 70 - < 90
				6 = 90 - 100
Lower 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.

[redacted]

‡ 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.

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

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

PASI 90 response: subjects achieving ≥ 90% improvement (reduction) in PASI score compared to Baseline are defined as PASI 90 responders

PASI 100 response/remission: complete clearing of psoriasis (PASI = 0)

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 8-3.

The definitions used in this study are based on Committee for Medicinal Products for Human Use (CHMP) guidelines for psoriasis (CHMP/EWP/2454/02 2004).

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 Period 1, at Visit week 12.

8.3.3 Appropriateness of efficacy assessments

PASI scores outcome measures, the assessment of the severity of the psoriasis symptoms and the extent to which the subject's body area is affected by the disease, is mandated by the European Medicines Agency (EMA) for the clinical investigation of medicinal products for the treatment of psoriasis (CHMP/EWP/2454/02 2004).

As indicated in Section 8.3.1, the IGA mod 2011 scale has been developed by Novartis in collaboration with Health Authorities, in particular the US FDA (Langley et al 2015). It has been used in phase III, IIIb, and IV secukinumab 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.

8.4 Safety/Tolerability

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

Blood withdrawals and safety assessments should be done prior to study treatment administration and should be taken as shown in Table 8-1 and in Appendix 2.

[redacted]

Appropriate safety assessments (eg, evaluation of AEs and SAEs including injection site reactions) should be repeated after the dose is administered. For details on AE collection and reporting, refer to AE section (Section 10).

Table 8-4 Physical Assessments

Assessment	Specification
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 8-1. 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. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the eCRF. Significant findings made after first administration of investigational drug which meet the definition of an AE must be recorded on the Adverse Event section of the eCRF
Vital signs	Vital signs (including blood pressure and pulse measurements) will be assessed at every scheduled visit as indicated in Table 8-1. 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 section. 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 bpm(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.
Height and weight	Height and body weight will be measured as listed in Table 8-1. Height and body weight will be measured in indoor clothing, but without shoes. Whenever, possible, body weight assessments should be performed by the same study site staff member; the same scale should be used throughout the study.

[redacted]

8.4.1 Laboratory evaluations

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

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

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

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

8.4.1.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count will be measured at all scheduled study visits, within the visit window suggested in Table 8-1.

8.4.1.2 Clinical chemistry

Serum chemistry will include urea, creatinine, total bilirubin, Aspartate Aminotransferase AST (SGOT), Alanine Aminotransferase ALT (SGPT), Gamma-Glutamyl Transferase (GGT), alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, and uric acid. Serum chemistry will be measured at all scheduled study visits within the visit window specified in Table 8-1.

8.4.1.3 Fasting Laboratory evaluations

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

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

8.4.1.3.1 Plasma glucose

Fasting blood sample will be collected for measuring fasting plasma glucose as indicated in Table 8-1.

8.4.1.3.2 Lipid panel

A lipid profile including High Density Lipoprotein, Low Density Lipoprotein, cholesterol, triglycerides, will be measured from a fasting blood sample as indicated in Table 8-1.

[redacted]

8.4.1.4 Urinalysis

Dipsticks will be provided to the study sites for local urinalysis assessments. The sites will record the results in the appropriate CRF for each subject. Standard dipstick measurements for specific gravity, protein, glucose, pH, blood, urine blood dipstick (non-hemolyzed), urine blood dipstick (hemolyzed), bilirubin, ketones and WBC will be done as indicated in Table 8-1.

If needed conditional microscopy assessments will be performed.

Documentation related to urinalysis including results must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included on appropriate eCRF page. Significant findings made after first administration of investigational drug which meet the definition of an AE must be recorded on the appropriate eCRF page.

8.4.2 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 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 CRF capturing medical history/ Current medical conditions/AE as appropriate.

8.4.3 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 8-1.

Any woman with a confirmed positive pregnancy test during Screening is not eligible for randomization. A positive urine pregnancy test during the treatment periods of the study requires immediate interruption of study treatment until a serum β-hCG (Human Chorionic Gonadotropin) 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.

8.4.4 Appropriateness of safety measurements

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

8.5 Additional assessments

The following additional assessments will be performed:

- Clinician Reported Outcomes (ClinRO)
  - Usability and hazard assessment of the auto-injector
- Patient Reported Outcomes (PRO)
  - SIAQ
  - DLQI
- [redacted]

8.5.1 Clinical Outcome Assessments (COAs)

Clinician Reported Outcomes (ClinRO)

Usability and hazard assessment of the auto-injector

The goal is to measure and evaluate the usability of the auto-injector during observed use, as well as the assessment of the hazards with the auto-injector.

Subjects will be instructed at Randomization through the site staff on how to self-inject via AI (and PFS) following the IFU. After explanations/instructions, the injection will be self-

[redacted]

administered by the subject into the appropriate injection site of the body. The delivery of the dose with the 2mL AI will be observed by investigator/site staff based on the 2 assessment check lists (see Table 8-5 and Table 8-6) at Randomization and Visit Week 1. Assessment of possible administration hazards will be based on identified hazards list (Table 8-6) as well as non-directed querying for any observed problems during self-injection.

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 IFU on how to self-inject via AI (and PFS). 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 self-injections at the respective visits (Randomization and Week 1) site staff will observe and complete the 2mL self-injection assessment checklist (Table 8-5) and the possible hazard assessment check list (Table 8-6) for the auto-injector.

The primary usability variables will be assessed based on binary (performed correctly: yes/no) response for the self-injection assessment check list. 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.

Table 8-5 Self-injection assessment check list (auto-injector)

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 auto-injector from the outer box	No
P4	Checked expiration date on auto-injector label	No
P5	Inspected the auto-injector for damage	No
P6	Inspected liquid for brown discoloration or particles	No
P7	Removed cap from auto-injector	Yes
P8	Discarded cap	No
P9	Hold the auto-injector at correct angle to the injection site	Yes
P10	Press the auto-injector firmly against the skin to trigger the injection (1st Click), and keep holding the auto-injector firmly against the skin	Yes
P11	Wait until the injection is complete, confirmed by the 2nd “click” and/or a check that the yellow indicator fills the window	Yes
P12	The auto-injector can now be removed	No
P13	Check again that the yellow indicator fills the window	No
P14	Disposed used auto-injector in a sharps container	No

[redacted]

Table 8-6 Possible hazard assessment check list (auto-injector)

No.	Possible Use-related hazards
H1	Was there a needle stick in a critical area (eg, 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?
H8	Was any other problem observed?[3]
H9	Was less than the full dose administered?[4]

The following potential hazards from the Hazards Identified List ([AIN457_HID_Delta225-01]) have not been included as not being observable during self-injection observation: microbiological contamination, wrong drug, transfer of transmissible diseases.

[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 (eg, 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, eg, 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 auto-injector 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 auto-injector 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, 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.

[redacted]

Primary usability assessment:

This consist of the assessment of successful 2mL AI **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 "required to be completed for successful administration" are identified in Table 8-5, these 4 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:

- This consist of the assessment of 2mL AI **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 2mL AI 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 8-5 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 8-6) will be computed by visit.
- This consist of the 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.

8.5.1.1 Patient Reported Outcomes (PRO)

All subjects will complete the PRO questions via an electronic tablet. The subject should be given sufficient space and time to complete the questionnaires. In case of any issues with tablet use, which cannot be resolved within the visit time window subject can complete PRO questions on paper form. If subject experiences any difficulties with submission after they complete the PROs, the study staff should assist with submitting the PRO responses. Attempts should be made to collect responses to all PROs for all subjects, including from those who prematurely discontinue prior to the study evaluation completion visit, however, if subjects refuse to complete PROs, this should be documented in study source records. Subject's refusal to complete study PROs are not protocol deviations.

8.5.1.1.1 Self-Injection Assessment Questionnaire (SIAQ)

The SIAQ measures the overall subject experience with subcutaneous self-injection, and to investigate the psychometric properties (Keininger and Coteur 2011, Appendix 4). The SIAQ

[redacted]

will be performed as a summary assessment for the auto-injector as outlined in the visit schedule (see Table 8-1).

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 2 mL AI self-injections and before the 1 mL PFS injections at the self-injections as the visits indicated in Table 8-1, including Randomization.

The PRE module includes 7 items grouped into three domains: Feelings about injections, Self-confidence and Satisfaction with self-injection (see Appendix 4)

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.

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 the 2 mL AI dosing but before the 1 mL PFS injection (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 8-1.

8.5.1.1.2 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 DLQI.

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

It will be completed in the language the respondent is most familiar with. The subject should be given sufficient space and time to complete the questionnaires. The study coordinator should check it 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 (IGA mod 2011, PASI), 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

[redacted]

10 of the protocol. Investigator should not encourage the subject to change the responses reported in the completed questionnaires.

The 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 8-1.

8.5.1.2 Trial Feedback

Not applicable.

8.5.1.3 Performance Outcomes (PerfO)

Not applicable.

8.5.1.4 Observer Reported Outcomes (ObsRO)

Not applicable.

8.5.1.5 Proxy Reported Outcomes

Not applicable.

[redacted]

[redacted]

8.5.3 Biomarkers

Not applicable.

8.5.4 Other assessments

No additional tests will be performed on subjects entered into this study.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 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 anytime.

[redacted]

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 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 participation in the study
- Pregnancy (Section 10.1.4)
- Ongoing use of prohibited treatment as shown in Table 6-1
- Any situation in which study participation might result in a safety risk to the subject
- Emergency unblinding

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information on the appropriate eCRF page.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (eg, telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

At the time of the study treatment discontinuation,

- if it has been approximately 4 weeks post last dose of study treatment, then the assessments described in EOT1 or EOT2/EOS should be completed.
- if it has not been approximately 4 weeks post last dose of study treatment, then the subject should be scheduled to return 4 weeks post last dose for their EOT1 assessments or EOT2/EOS assessments.

Assessments detailed in Table 8-1 should be completed and recorded in the eCRF.

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.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

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

[redacted]

The investigator must also contact the IRT when the subject completes EOT1 or EOT2/EOS visit to register the subject's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

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

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

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

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

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 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 (including

[redacted]

slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) 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 or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit (Visit Week 52), and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision (eg, each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (eg, 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.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions and problems.

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 (Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB)) 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.

[redacted]

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

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

1. 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
2. its relationship to the study treatment (suspected: Yes / No)
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a serious adverse event SAE – (See Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. action taken regarding study treatment.
   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/withdrawn
6. its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown
7. concomitant medication or non-drug therapy given
8. subject hospitalized/subject's hospitalization prolonged (see Section 10.1.2 for definition of SAE)

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 CRF capturing adverse events. Exceptions include cases when a) a new type of psoriasis is diagnosed eg, 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 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.

10.1.2 Serious adverse events

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - 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, eg, defined as an event that jeopardizes the subject or may require medical or surgical intervention.

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

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

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

[redacted]

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

10.1.3 SAE reporting

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

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

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

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

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

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

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

[redacted]

10.1.4 Pregnancy reporting

Pregnancies

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 Novartis Chief Medical Office and Patient Safety (CMO & PS) Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

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

10.1.5 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 recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

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

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

[redacted]

10.2 Additional Safety Monitoring

Not applicable.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs) using fully validated secure web-enabled software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

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

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

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

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

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

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

Subjects will fill in their PRO data in a site based tablet. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

[redacted]

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

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

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/ representative will review the protocol and data capture requirements (i.e., eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and 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 data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. 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 give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all subject data up to Week 16 for the week 16 interim analysis and on all data at the time of the trial ends for the final analysis. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Treatment groups for analyses will include:

Primary Week 12 analysis:

- secukinumab 300 mg (2 mL AI)
- secukinumab 300 mg (2 x 1 mL PFS)

[redacted]

- placebo

Entire study:

- secukinumab 300 mg (2 mL AI)
- secukinumab 300 mg (2 x 1 mL PFS)
- placebo switched secukinumab 300 mg (2 mL AI)
- placebo switched secukinumab 300 mg (2 x 1 mL PFS)
- any secukinumab 300 mg (2 mL AI)
- any secukinumab 300 mg (2 x 1 mL PFS)
- any secukinumab 300 mg
- placebo

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.

12.1 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 at baseline visit. Unless otherwise specified, subjects with missing informed consent form as well as mis-randomized subjects (mis-randomized in IRT) will be excluded from the randomized set. (Mis-randomized subjects are subjects who are screen-failures, but have been randomized by the investigator before eligibility was finally assessed, however have not been treated. If subjects were re-screened and successfully randomized, they will be included in the randomized set according to the treatment assigned in the last randomization.).

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

Safety set: 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.

12.2 Subject demographics and other baseline characteristics

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

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.

Medical history

[redacted]

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.

12.3 Treatments

12.3.1 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 (eg, 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 from placebo to active treatment) or minimum of last dose of the treatment + 84 days and last visit date.

12.3.2 Prior and concomitant medication

Prior and concomitant medications will be summarized by treatment group for the different periods 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.

12.4 Analysis of the primary variables

Details of the testing strategy including primary endpoints are provided in Section 12.4.2.

12.4.1 Definition of primary endpoint(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 FAS.

[redacted]

12.4.2 Statistical model, hypothesis, and method of analysis

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

The statistical hypothesis is that secukinumab 300 mg (2 mL AI) 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 AI)

The following hypothesis 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 AI) is not superior to placebo with respect to PASI 75 response at Week 12

H_2: Secukinumab 300 mg (2 mL AI) 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 logistic regression with treatment group (secukinumab 2mL AI vs Placebo); baseline bodyweight strata and baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons of secukinumab dose regimen versus placebo 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.

If logistic regression model does not converge the following steps will be performed:

1. Run the PROC GENMOD procedure with EXACT statement;
2. If convergence not reached, remove the covariates from the model one by one until convergence is reached; start with continuous covariates (baselines PASI score), followed by removing categorical covariates (i.e., weight stratum etc.,);
3. If convergence not reached, perform Fisher's exact test.

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 AI) has not been demonstrated.

[redacted]

12.4.3 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. 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 (eg, premature study discontinuation, missed visit, administrative issues), exceptions will apply to the following:
  - If a subject dropped out of the study prior to last scheduled efficacy assessment and being responder consecutively at least for two preceding visits, the subject will be imputed as responder for the last scheduled visit.
  - If a subject who was responder at visit x-1 and visit x+1 but has missing data at visit x, then the subject will be imputed as responder for visit x as long as the distance between the scheduled visits *x*-1 and *x* is 4 weeks or less, or the distance between the scheduled visits *x* and *x*+1 is 4 weeks or less. Otherwise missing data will be imputed with non-response.

12.4.4 Sensitivity analyses

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

12.5 Analysis of secondary endpoints

The key secondary endpoint of this study is PASI 90 response at Week 12.

Testing strategy

As stated in Section 12.4.2, the hypotheses H_1 and H_2 will be included in co-primary testing procedure. Each hypotheses is tested at $\alpha = 2.5\%$ (one-sided). The testing sequence will continue to key secondary endpoint PASI 90 at $\alpha = 2.5\%$ (one-sided) only if both H_1 and H_2 have been rejected at α (one-sided) such that a family-wise type-I-error of α (one-sided) is kept.

H_3: secukinumab 300 mg (2 mL AI) is not superior to placebo with respect to PASI 90 response at Week 12

PASI 90 response will be analyzed analogously to the primary endpoints at Week 12, i.e., the logistic regression model with treatment group, baseline bodyweight strata and baseline PASI score as exploratory variables. Odds ratios will be computed for comparisons of secukinumab versus placebo utilizing the logistic regression model fitted.

[redacted]

12.6 Analysis of other secondary and exploratory endpoints

12.6.1 Efficacy Endpoints

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, comparisons between 2mL AI vs placebo and 2mL AI vs 1mL PFS x 2 will be conducted using 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.

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.

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.

12.6.2 Safety Endpoints

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.

Adverse events

Treatment emergent 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 Period 1 and for the entire study (Treatment Period 1 combined with Treatment Period 2)

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 periods.

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 (CTC) 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]

[redacted]

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).

12.6.3 Health-related Quality of Life - Dermatology Life Quality Index (DLQI)

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

[redacted]

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 will be the stratum 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.

12.6.4 Self-Injection Assessment 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 (Feeling about injections, Self-confidence domains and overall satisfaction of self-injection item) from the POST module taken after self-injections. Change from the PRE module to POST module in item and domain scores will be summarized by visit and treatment group.

12.6.5 Resource utilization

Not applicable.

[redacted]

12.6.7 DNA

Not applicable.

[redacted]

12.6.8 Biomarkers

Not applicable.

[redacted]

12.7 Interim analyses

A Week 16 analysis will be performed when all subjects have completed the Visit Week 16. Additional interim analyses may be performed to support health authority interactions as necessary. Trial modifications are not planned based on any interim analysis.

At the end of study, a final analysis of all data collected up to last study visit (Week 52) will be performed when all subjects have completed the last study visit.

12.8 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 auto-injector s.c.) group.

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

12.8.1 Primary endpoint(s)

With respect to the co-primary endpoints (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 40 subjects per group and assuming a response rate of 8% 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 auto-injector s.c.) group based on Fisher's exact test (nQuery Advisor 7.01, two group Fisher's-exact test of equal proportions) is above 99% for PASI 75 response and IGA mod 2011 0 or 1 response.

12.8.2 Secondary endpoint(s)

The study should be sufficiently powered (above 90%) to show a response rate of 46% points in PASI 90 response if the placebo rate is assumed as 8%.

13 Ethical considerations and administrative procedures

13.1 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

[redacted]

local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 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 (eg, 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.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (eg, Clinicaltrials.gov, EudraCT etc.)

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

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

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

14 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 including

[redacted]

incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis/sponsor health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

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[redacted]

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests. Notable values for blood pressure and pulse are presented in Table 8-4.

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

[redacted]

[redacted]

[redacted]

16.3 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).

[redacted]

2. The transformed scores for items contributing to a domain are then averaged into a domain score.

Table 16-3 Scoring of SIAQ 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		

[redacted]

16.4 Appendix 4: SIAQ Questionnaire

Representative examples

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

[redacted]

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

[redacted]

SELF-INJECTION ASSESSMENT QUESTIONNAIRE (SIAQ)

- POST-Self-Injection -

INTRODUCTION

The following questions concern the self-injection of your medication and must be answered after 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.

FEELINGS ABOUT INJECTIONS

The following questions concern your **feelings about injections**.

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
☐	☐	☐	☐	☐

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

Not at all	A little	Moderately	Very	Extremely
☐	☐	☐	☐	☐

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

Not at all	A little	Moderately	Very	Extremely
☐	☐	☐	☐	☐

[redacted]

SELF-IMAGE

The following question concerns your **self-image**.

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

4. How embarrassed would you feel if someone saw you with the self-injection device?

Not at all	A little	Moderately	Very	Extremely
☐	☐	☐	☐	☐

SELF-CONFIDENCE

The following questions concern your **confidence** about giving yourself an injection.

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

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

Not at all	A little	Moderately	Very	Extremely
☐	☐	☐	☐	☐

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

Not at all	A little	Moderately	Very	Extremely
☐	☐	☐	☐	☐

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

Not at all	A little	Moderately	Very	Extremely
☐	☐	☐	☐	☐

[redacted]

PAIN AND SKIN REACTIONS DURING OR AFTER THE INJECTION

The following questions ask about **pain and skin reactions** you may have experienced during or after the injection.

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

8. During and/or after the injection, how bothered were you by:	Not at all	A little	Moderately	Very	Extremely
a. **pain**?	☐	☐	☐	☐	☐
b. **burning sensation**?	☐	☐	☐	☐	☐
c. **cold sensation**?	☐	☐	☐	☐	☐

9. During and/or after the injection, how bothered were you by:	Not at all	A little	Moderately	Very	Extremely
a. **itching** at the injection site?	☐	☐	☐	☐	☐
b. **redness** at the injection site?	☐	☐	☐	☐	☐
c. **swelling** at the injection site?	☐	☐	☐	☐	☐
d. **bruising** at the injection site?	☐	☐	☐	☐	☐
e. **hardening** at the injection site?	☐	☐	☐	☐	☐

[redacted]

EASE OF USE OF THE SELF-INJECTION DEVICE

The following questions ask about the **ease of use** of the self-injection device.

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

How difficult or easy was it to:	Very difficult	Difficult	Somewhat difficult	Somewhat easy	Easy	Very easy
10. remove the cap?	☐	☐	☐	☐	☐	☐
11. depress the plunger or button on the device?	☐	☐	☐	☐	☐	☐
12. administer the injection without any help?	☐	☐	☐	☐	☐	☐
13. use the self-injection device?	☐	☐	☐	☐	☐	☐

14. How does the device fit in your hand?

Very uncomfortably	Uncomfortably	Somewhat uncomfortably	Somewhat comfortably	Comfortably	Very comfortably
☐	☐	☐	☐	☐	☐

SATISFACTION WITH SELF-INJECTION

The following questions ask about your **satisfaction** with self-injection.

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

15. How easy was it to give yourself an injection?

Not at all	A little	Moderately	Very	Extremely
☐	☐	☐	☐	☐

16. How satisfied are you with **how often** you give yourself an injection?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
☐	☐	☐	☐	☐

[redacted]

17. How satisfied are you with the **time it takes to inject** the medication?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
☐	☐	☐	☐	☐

18. Overall, how satisfied are you with your current way of taking your medication (self-injection)?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
☐	☐	☐	☐	☐

19. Overall, how convenient is the self-injection device?

Very inconvenient	Inconvenient	Neither inconvenient nor convenient	Convenient	Very convenient
☐	☐	☐	☐	☐

20. After this study, would you choose to continue self-injecting your medication?

Definitely not	Probably not	I don't know	Yes, probably	Yes, definitely
☐	☐	☐	☐	☐

21. After this study, how confident would you be to give yourself injections at home?

Not at all	A little	Moderately	Very	Extremely
☐	☐	☐	☐	☐

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

[redacted]

16.5 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.

[redacted]

16.6 Appendix 6: Determination of Tuberculosis status

Determination of tuberculosis (TB) status will be required before administration of study treatment and should be performed as defined by local guidelines. TB status must be determined by medical history, signs, symptoms and TB central lab testing. Any significant findings will be recorded in the relevant TB assessment eCRF and the Medical History eCRF, as necessary.

A central lab testing will be performed to assess the TB status at screening for all subjects. This test will only be used to determine subject's eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection (Doherty et al 2008).

This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin vaccination or 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 tuberculosis 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 16-1.

a. If the test result is **negative**, the subject may be randomized.

b. 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.

c. 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.

   i. If the second test is negative, the subject may be randomized.

   ii. If the second test is positive or indeterminate, the investigator should perform workup as per local guidelines. Subject positive for **latent** TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration. The subject will not be

[redacted]

eligible for randomization if “active tuberculosis is present” or “latent tuberculosis is present” and is untreated per local guidelines. .

iii. Subjects negative for TB per workup (no signs of latent or active TB) may be randomized to the trial if the workup 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 Period (within 4 weeks prior to randomization) and TB work-up will only be considered if it was completed **within 12 weeks** prior to randomization.

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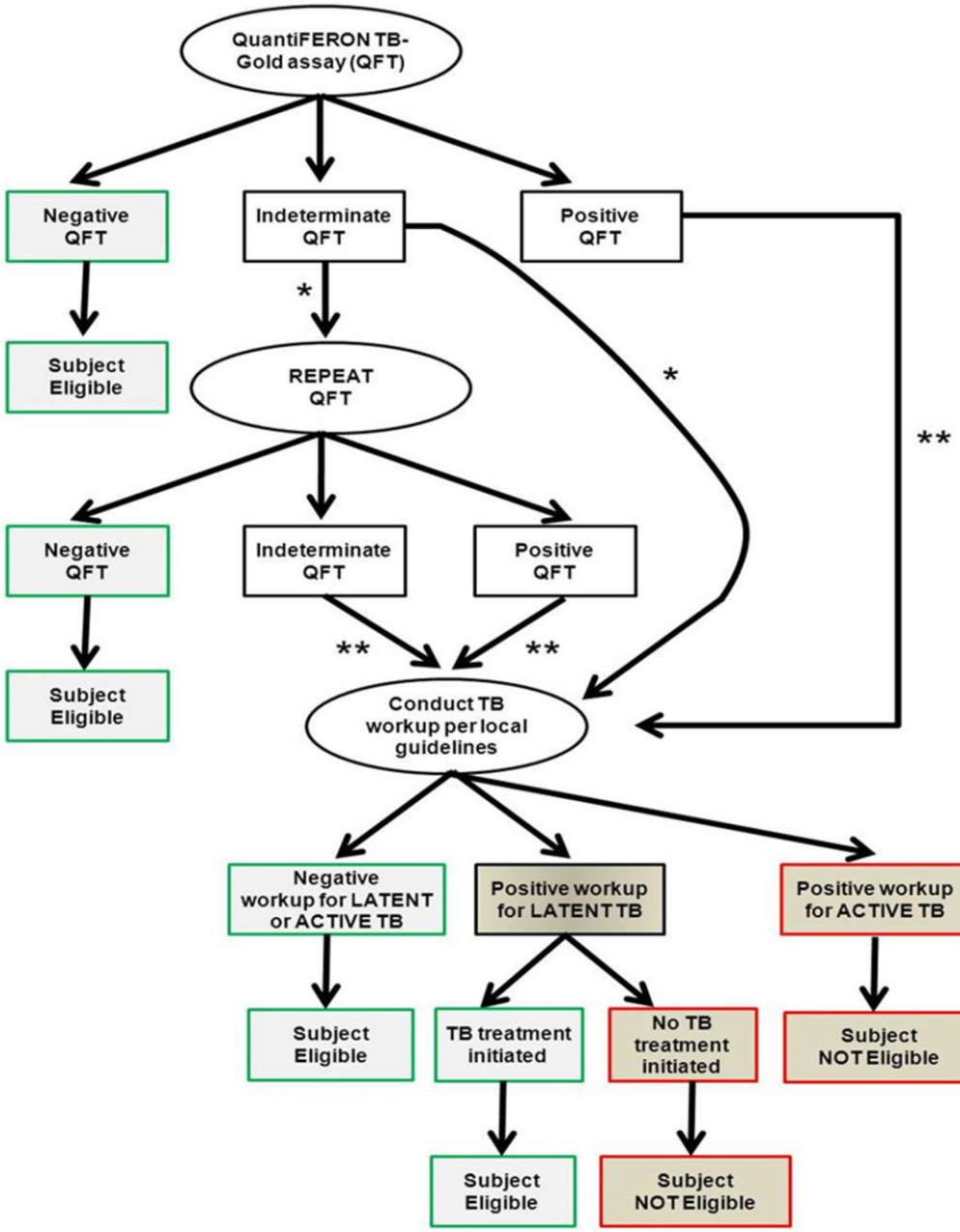
[redacted]

Figure 16-1 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).

[redacted]