

Clinical Development – Medical Affairs Region Europe

Cosentyx[®]/Secukinumab/AIN457

Clinical Trial Protocol CAIN457A3401 / NCT02752776

An open-label, prospective, non-randomized, multicenter study to evaluate clear skin effect on health-related quality of life outcomes at 16 and 52 weeks in patients with moderate to severe plaque psoriasis treated with secukinumab 300 mg s.c. with or without previous exposure to systemic therapy

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Document type: Clinical Trial Protocol

EUDRACT number: 2015-003701-42

Version number: v00 (Original protocol)

Development phase: Phase 4

Release date: 21-Oct-2015

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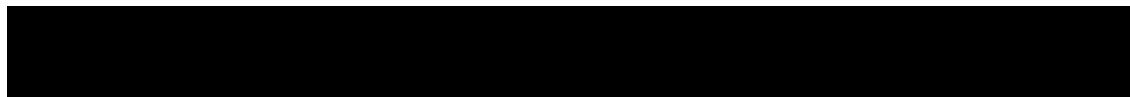
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Clinical Trial Protocol Template Version 2.0, November, 2013

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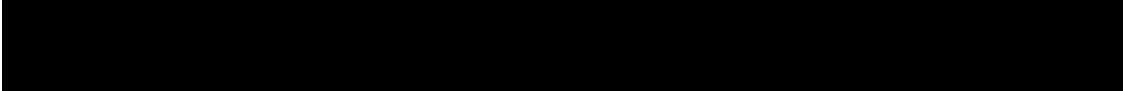
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List of abbreviations

AE	Adverse Event
AIN457	Secukinumab
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
bpm	Beats per Minute
BSA	Body Surface Area
CHMP	Committee for Medicinal Products for Human Use
CRF	Case Report Form (paper or electronic)
CRO	Contract Research Organization
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOT	End of Treatment
EQ-5D	EuroQoL 5-Dimension Health Questionnaire [®]
	
GCP	Good Clinical Practice
H	Head (PASI scoring system)
hCG	Human Chorionic Gonadotropin
HAQ [®] -DI	Health Assessment Questionnaire [®] -Disability Index
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for Use
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011

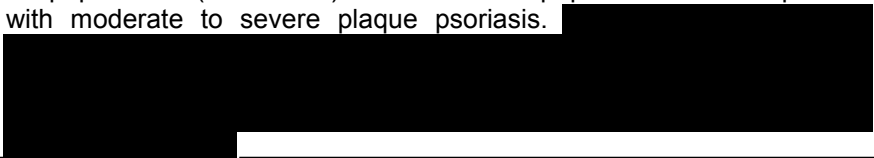



IL	Interleukin
IN	Investigator Notification
IRB	Institutional Review Board
L	Lower limbs (PASI scoring system)
LLN	Lower Limit of Normal
LPFT	Last Patient First Treatment
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric Rating Scale
NYHA	New York Heart Association
PASI	Psoriasis Area and Severity Index
PBI	Patient Benefit Index
PRO	Patient Reported Outcomes
PsA	Psoriatic Arthritis
PUVA	Psoralen Ultraviolet A
QFT	Quantiferon TB-Gold Test
QoL	Quality of Life
SAE	Serious Adverse Event
s.c.	Subcutaneous, subcutaneously
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Trunk (PASI scoring system)
TB	Tuberculosis
TCS	Topical Corticosteroid
TSQM	Treatment Satisfaction Questionnaire for Medication
U	Upper limbs (PASI scoring system)
ULN	Upper Limit of Normal
UV	Ultraviolet
UVB	Ultraviolet B
WBC	White Blood Cells
WHO	World Health Organization


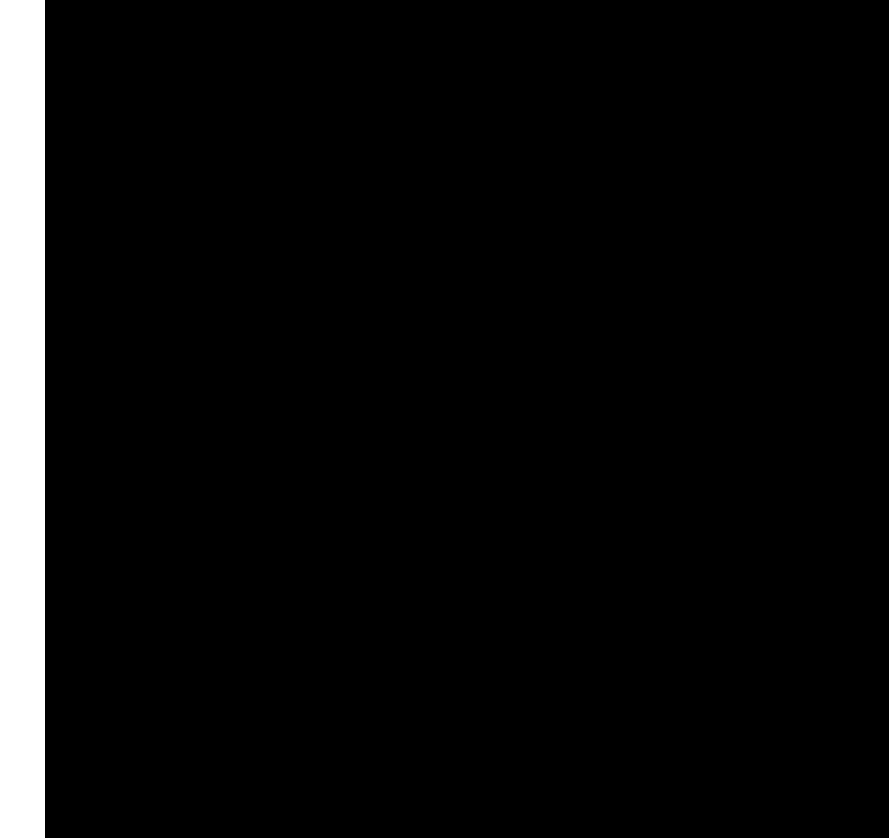
Glossary of terms

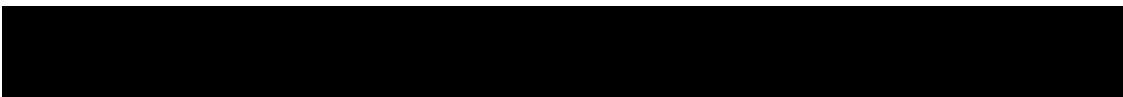
Assessment	A procedure used to generate data required by the study.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained prior to starting any of the procedures described in the protocol.
Medication number	A unique identifier on the label of each investigational/study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

Protocol summary

Protocol number	CAIN457A3401
Title	An open-label, prospective, non-randomized, multicenter study to evaluate clear skin effect on health-related quality of life outcomes at 16 and 52 weeks in patients with moderate to severe plaque psoriasis treated with secukinumab 300 mg s.c. with or without previous exposure to systemic therapy.
Brief title	Study of effects of secukinumab on quality of life (QoL) in psoriasis patients with or without prior exposure to systemic therapy.
Sponsor and Clinical Phase	Novartis, Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	<p>Understanding the patient's perspective on their disease and treatment is an important component of clinical research and medical practice. Secukinumab 300 mg s.c. is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Candidates for systemic therapy can be divided into 3 sub-populations:</p> <ul style="list-style-type: none">• Subpopulation A: Patients who are naïve to any systemic treatment, e.g. patients failing or intolerant to previous topical treatment, including narrow band ultraviolet B (UVB) but never exposed to any systemic treatment, with or without contraindications to the use of conventional systemic treatment and in need of a first systemic treatment.• Subpopulation B: Patients who have been previously exposed to at least one conventional systemic therapy; either because of failure or intolerance to their previous conventional systemic treatment, they are in need of first biologic systemic treatment.• Subpopulation C: Patients who have been previously exposed to at least one biologic systemic therapy; either because of failure or intolerance to their previous biologic systemic treatment, they are in need of a different biologic systemic treatment. <p>The purpose of this patient centric study is to assess the impact of the exposure to a previous treatment prior to starting treatment with secukinumab 300 mg s.c. on QoL outcomes in relation to the highest skin efficacy response expected at Week 16 and the skin efficacy response at Week 52. The study population will consist of 3 pre-identified subpopulations (see above) and the overall population of these patients with moderate to severe plaque psoriasis.</p> 



Primary Objective	<ul style="list-style-type: none">• To assess the proportion of patients achieving a Dermatology Life Quality Index (DLQI) 0/1 response at Week 16 in 3 pre-defined subpopulations and in the overall study population.
Secondary Objectives	<ul style="list-style-type: none">• To assess the proportion of patients achieving a DLQI 0/1 response at Week 52 in 3 pre-defined subpopulations and in the overall study population.• To assess the effects of treatment with secukinumab 300 mg with respect to changes in EuroQoL 5-Dimension Health Questionnaire[®] (EQ-5D[®]), Health Assessment Questionnaire[®]-Disability Index (HAQ[®]-DI), Numeric Rating Scale (NRS), Treatment Satisfaction Questionnaire for Medication (TSQM) and Patient Benefit Index (PBI) response over time up to Week 16 and Week 52 compared to Baseline in 3 pre-defined subpopulations and in the overall study population.• To assess the proportion of patients achieving psoriasis area and severity index (PASI) 50, PASI 75, PASI 90, PASI 100 and Investigator's Global Assessment modified 2011 (IGA mod 2011) 0/1 responses at Week 16 and Week 52 in 3 pre-defined subpopulations and in the overall study population.• To assess the proportion of patients with DLQI scores 2-5, 6-10, 11-20, 21-30 at Week 16 and Week 52 compared to Baseline in 3 pre-defined subpopulations and in the overall study population.• To assess the overall safety and tolerability of treatment with secukinumab 300 mg in 3 pre-defined subpopulations and in the overall study population.
	



Study design	<p>This is an open-label, prospective, non-randomized, multicenter study of secukinumab 300 mg s.c. in patients with moderate to severe plaque psoriasis with or without previous exposure to systemic therapy. The study will take place across Europe in approximately 250 study centers in 30 European countries. The study will be implemented in both hospital-based and office-based investigational sites. Secukinumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis and whose center fulfills International Conference on Harmonization (ICH) Good Clinical Practice (GCP) quality requirements for the conduct of clinical trials.</p>
Population	<p>The study population will consist of a representative group of male and female patients (≥ 18 years old) with moderate to severe plaque psoriasis. Moderate to severe plaque-type psoriasis is defined as a total PASI score of ≥ 10, IGA mod 2011 ≥ 3 and a body surface area (BSA) ≥ 10% at Baseline. Prior to entering the study, patients may either be naïve to systemic treatment (with or without contraindications to conventional systemic treatments) or have had prior exposure to any systemic therapy (conventional or biologic) used to treat their psoriasis. Patients may have received topical treatment and narrow band UVB treatment prior to study entry.</p>
Inclusion criteria	<ul style="list-style-type: none"> • Patients must be able to understand and communicate with the Investigator and comply with the requirements of the study (including administration of secukinumab s.c. injections at home) and must provide 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. • Men or women aged at least 18 years at time of Screening. • Moderate to severe plaque-type psoriasis diagnosed for at least 3 months prior to Screening and candidate for systemic therapy. • Moderate to severe plaque-type psoriasis is defined at Baseline by: <ul style="list-style-type: none"> - PASI score ≥ 10 <u>and</u> - IGA mod 2011 score ≥ 3 <u>and</u> - BSA ≥ 10% • Candidate for systemic therapy is defined as a patient having moderate to severe plaque-type psoriasis that is inadequately controlled by: <ul style="list-style-type: none"> - Topical treatment (patients who were naïve to systemic treatments). - Phototherapy and/or previous systemic therapy (systemic therapy could be either conventional or biologic).
Exclusion criteria	<ul style="list-style-type: none"> • Forms of psoriasis other than moderate to severe plaque-type psoriasis, e.g. drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium) at Screening.



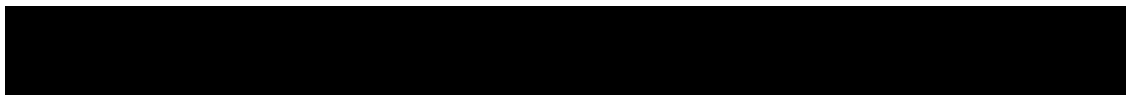
	<ul style="list-style-type: none">• Patients with previous treatment with any agent targeting interleukin (IL)-17 directly or IL-17 receptor A (e.g. secukinumab, ixekizumab, or brodalumab).• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (> 5 mIU/mL).• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant unless they use effective contraception during the entire study or longer if required by locally approved prescribing information (e.g. 20 weeks in EU). Barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide (where available). Note: spermicides alone are not a barrier method of contraception and should not be used alone. The following methods are considered more effective than the barrier method and are also acceptable:<ul style="list-style-type: none">- Total abstinence: When this is in line with the preferred and usual lifestyle of the patient (periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods or withdrawal are not acceptable methods of contraception).- Female sterilization: have had a surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.- Male partner sterilization at least 6 months prior to Screening. For female patients on the study, the vasectomized male partner should be the sole partner for that patient.- Use of established oral, injected or implanted hormonal methods of contraception, intrauterine device or intrauterine system post-ovulation methods).NOTE: Women are considered post-menopausal and not of child bearing potential if they have had:<ul style="list-style-type: none">- 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or- 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [for US only: and estradiol < 20 pg/mL] or- Surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.• Active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of secukinumab therapy.
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	<ul style="list-style-type: none">• Underlying condition (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 patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy. Patients who are treated with secukinumab and have Crohn's disease are eligible but should be followed closely.• Investigator discretion should be used for patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders.• Significant medical problems including but not limited to the following: uncontrolled hypertension (systolic ≥ 160 mmHg and/or diastolic ≥ 95 mmHg), congestive heart failure (New York Heart Association (NYHA) status of class III or IV).• Patients with a serum creatinine level exceeding 176.8 $\mu\text{mol/L}$ (2.0 mg/dL).• Screening total white blood cell (WBC) count $< 2\,500/\mu\text{L}$, or platelets $< 100\,000/\mu\text{L}$ or neutrophils $< 1\,500/\mu\text{L}$ or hemoglobin < 8.5 g/dL.• Active systemic infections during the last 2 weeks (exception: common cold) prior to Baseline and any infections that reoccur on a regular basis; Investigator discretion should be used regarding patients who have travelled or resided in areas of endemic mycoses, such as histoplasmosis, coccidioidomycosis or blastomycosis and for patients with underlying conditions that may predispose them to infection, such as advanced or poorly controlled diabetes.• History of an ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by a positive or indeterminate QuantiFERON TB-Gold test (QFT) at Screening. Patients with a positive or indeterminate QFT test may participate in the study if a full tuberculosis (TB) work-up (according to local practice/guidelines) completed within 12 weeks prior to Day 1 (Baseline) establishes conclusively that the patient has no evidence of active TB. If presence of latent TB is established then treatment must have been initiated and maintained according to local country guidelines prior to Day 1 (Baseline).• Past medical history record of, or current infection with, human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus prior to Baseline.• History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for Bowen's disease of the skin, or basal cell carcinoma or actinic keratosis 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).• Current severe progressive or uncontrolled disease, which in the judgment of the clinical Investigator renders the patient unsuitable for the study or puts the patient at increased risk (e.g. myocardial infarction within 26 weeks prior to Baseline).
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	<ul style="list-style-type: none"> • Inability or unwillingness to undergo repeated venipuncture (e.g. because of poor tolerability or lack of access to veins) or self-injection with pre-filled syringes (PFSs). • Patients who are allergic to rubber or latex or with history of hypersensitivity reactions to any of the excipients. • 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. • History or evidence of ongoing alcohol or drug abuse within the last 6 months before Baseline. • Plan for administration of live vaccines during the study period or 6 weeks prior to Baseline. • Use of investigational treatment within 4 weeks before Baseline, or within a period of 5 half-lives of the investigational treatment, whichever is longer. • Patients not willing to limit UV light exposure (e.g. sunbathing and/or the use of tanning devices) during the course of the study.
<p>Investigational and reference therapy</p>	<p>Secukinumab 300 mg will be provided in 2 × 1 mL 150 mg secukinumab PFSs for s.c. injection. Secukinumab 300 mg (2 × PFSs of the 150 mg dose) will be self-administered by the patient at Baseline, once weekly at Weeks 1, 2 and 3, and thereafter at 4-weekly intervals starting from Week 4 until Week 16 (Treatment Period 1) or until Week 48 (Treatment Period 2).</p> <p>Patients will receive instructions for use (IFU) and training from study center staff on how to use and self-administer the study drug. The injections up to Week 16 and the subsequent ones occurring during a visit will be performed by the patient (or caregiver) at the study center, under the supervision of the study site staff. The injections not occurring during a study center visit will be performed by the patients (or caregiver) at their home. Training kits may be supplied by Novartis to study centers not familiar with use of PFS.</p>
<p>Efficacy assessments</p>	<ul style="list-style-type: none"> • Investigator's Global Assessment modified 2011 (IGA mod. 2011) • Psoriasis Area and Severity Index (PASI) • Body Surface Area (BSA)
<p>Safety assessments</p>	<ul style="list-style-type: none"> • Adverse events • Vital signs (e.g. pulse rate, blood pressure) • Laboratory assessments (e.g. hematology, chemistry, urine tests) • Physical examination
<p>Other assessments</p>	<p>Psoriasis / Psoriatic arthritis related questionnaires:</p> <ul style="list-style-type: none"> • Numeric Rating Scale (NRS) - itching, scaling and pain visual analog scale (VAS) • Health Assessment Questionnaire®-Disability Index (HAQ®-DI for patients with concomitant PsA only) • Treatment Satisfaction Questionnaire for Medication (TSQM)



	<ul style="list-style-type: none">• Patient Benefit Index (PBI) Dermatology related questionnaires: <ul style="list-style-type: none">• Dermatology Life Quality Index (DLQI)• [REDACTED] General health related questionnaire: <ul style="list-style-type: none">• EuroQoL 5-Dimension Health Status Questionnaire (EQ-5D[®])
Data analysis	<p>The primary analysis variable is the proportion of patients achieving a DLQI 0/1 response at Week 16 in subpopulations of patients with moderate to severe plaque psoriasis naïve to conventional systemic treatments, or previously exposed to at least one conventional or biologic systemic treatments for psoriasis, and in the overall study population.</p> <p>The primary analysis of this study will be purely descriptive without any formal group comparisons or hypothesis testing. For the proportions, (descriptive) 95% confidence intervals (CIs) will be reported additionally.</p>
Key words	Plaque psoriasis, DLQI, EQ-5D [®] , [REDACTED] HAQ [®] -DI, multicenter, NRS, PASI, PBI, psoriasis, QoL, secukinumab, TSQM



1 Introduction


1.1 Background

Psoriasis is an immune-mediated, chronic relapsing inflammatory disease that mainly affects the skin and is characterized by variable clinical features. Plaque (also called plaque-type or chronic plaque) psoriasis is the most frequent clinical presentation. Chronic plaque psoriasis can have a profound impact on several aspects of a patient's life. Psoriasis affects not only the skin itself but has been demonstrated to be closely related to the deterioration of patient's emotional, social, occupational, and physical functioning (Eskin et al 2014). The impact of untreated chronic psoriasis on quality of life (QoL) has been demonstrated to be similar to the effects of cancer or congestive heart failure (Bhutani et al 2013). For these reasons, understanding the patient's perspective on their psoriasis and impact on daily activities and disease treatment is a critical component of clinical research and practice.

Broadly accepted assessment systems to measure the effect of psoriasis treatments on patients through a clinician-reported outcome are the Psoriasis Area and Severity Index (PASI) or the Investigator Global Assessment (IGA) (Feldman et al 2005; Langley et al 2013). The correlation between clinician-reported outcomes and patient-reported outcomes (PROs) has been studied to some extent (Revicki et al 2008); however, a better understanding from the view of the patient on the individual impact on the disease, influencing factors and effect of secukinumab during short and long term treatment is needed. Several PRO measures are available for psoriasis evaluation and are starting to be included as valuable endpoints in clinical trials (Gniadecki et al 2012, Revicki et al 2007, Lebwohl et al 2010, and Viswanathan et al 2014). A combination of general health-related, dermatology-related and psoriasis-related questionnaires provides a comprehensive overview from different patient perspectives.

The EuroQOL 5-Dimension Health Questionnaire[®] (EQ-5D[®]) assesses each subject's overall health status and is a standardized tool for measuring health outcomes. It has been extensively used in several dermatological conditions including psoriasis (Rønneberg Mehren et al 2014). The tool was used during the Phase 3 clinical program for secukinumab.

The Dermatology Life Quality Index (DLQI) developed in 1994 (Finlay and Khan 1994), was the first dermatology-specific QoL instrument. Widely used (tested across >40 different skin conditions and available in >90 languages, Basra et al 2008); it is a self-administered assessment of 6 domains: daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school over the previous week. Several studies demonstrated a good correlation between the reduction in PASI score and the reduction in DLQI (Vender et al 2012, Driessen et al 2010). Secukinumab demonstrated clinically meaningful improvements in DLQI score in Phase 3 studies; however, the impact of previous psoriasis treatment on DLQI scoring has not yet investigated in depth.



In a large, multinational, population-based survey of psoriasis and/or PsA in North America and Europe, patients indicated that their most bothersome signs or symptoms were itching (43%) and scaling (23%) (Lebwohl et al 2014). The Numeric Rating Scale (NRS) is an 11-point visual analog scale (VAS) used to evaluate the patient assessment of their main skin symptoms and signs such as itching, scaling and pain.

Since psoriasis is an immune-mediated, chronic inflammatory disease, it may also result in systemic pathological effects. The severe forms have been associated with several diseases that have similar pathogenic factors. A comorbidity classically associated with psoriasis is psoriatic arthritis (PsA) (Moll et al 1973, Gladman 2004, Gladman et al 2005, Ibrahim et al 2009). The Health Assessment Questionnaire[®]-Disability Index (HAQ[®]-DI) assesses the long term influence of chronic disease on functional ability and activity restriction in patients with a history of PsA (Fries et al 1982). Eighteen percent of patients in the Phase 3 program reported concomitant PsA at Baseline hence confirmation from a large study would be important.

Treatment success is highly influenced by patient satisfaction, as demonstrated by several studies investigating treatment satisfaction in psoriatic patients treated with biologics. Although satisfaction with treatment was generally high, room for improvement was constantly detected in the “effectiveness” domain, which included the rapidity of onset of the clinical improvement in the “side-effects” and “convenience” domains of the Treatment Satisfaction Questionnaire for Medication (TSQM) (van Cranenburgh et al 2013, van den Reek et al 2014). The Patient Benefit Index (PBI) is a tool developed to assess patient relevant benefits in the treatment of psoriasis with a focus on perception of disease control; before treatment, the patient is asked about those benefits of treatment that are personally important to him/her; during or after treatment, the extent to which these patient-defined aims of treatment are being/were achieved is recorded (Feuerhahn et al 2012). Psoriasis is perceived by a significant number of patients as uncontrollable as well as incurable. This can trigger patient reactions such as anger or annoyance that might influence the perception of the treatment success (Linder et al 2009). Neither the TSQM nor PBI PROs were assessed during the Phase 3 clinical program for secukinumab.

Skin efficacy and QoL may be impacted by factors such as presence of co-morbidities (Henseler et al 1995, Christophers 2007, Naldi et al 2010, Augustin et al 2010), the duration of the disease (Ros et al 2014), the localization of the plaques (Finlay and Coles 1995, O’Neill et al 1996, Touw et al 2001), and a concomitant treatment with topical medications for psoriasis (Heydendael et al 2004, Paul et al 2011, Albrecht et al 2011). A deeper knowledge of the relevance of these factors will help clinicians in better managing their patients and meeting patient expectations.

Secukinumab (AIN457) is a recombinant high-affinity fully human monoclonal anti-human interleukin-17A (IL-17A) antibody of the IgG1/κ-class. Secukinumab binds to human IL-17A and neutralizes the bioactivity of this cytokine. IL-17A is the central lymphokine of a newly defined subset of inflammatory T cells, the Th17 cells which, in several animal models, are pivotal in several autoimmune and inflammatory processes. IL-17A is mainly produced by memory effector CD4+ and CD8+ T lymphocytes (Lowes et al 2008; Kagami et al 2010). In the skin, this cytokine acts principally on keratinocytes to induce their activation and proliferation (Nestle et al 2009). A recent study showed that neutrophils may also be a

relevant source of the inflammatory cytokine IL-17A in psoriasis lesions (Reich et al 2015). IL-17A is being recognized as one of the principal pro-inflammatory cytokines in immune mediated inflammatory diseases. Its neutralization is expected to treat the underlying pathophysiology of immune mediated disease and as a consequence provide relief of symptoms (Patel et al 2013). An extensive Phase 2/3 program conducted in 3 430 patients demonstrated secukinumab to be very effective in treating plaque psoriasis, with 300 mg being the dose that delivered the most clinically meaningful benefit to patients with respect to achievement of almost clear to clear skin, improved QoL, speed of onset of action, and sustainability of symptom relief. From a safety perspective, secukinumab was well tolerated. Secukinumab was approved in the European Union (EU) in January 2015 for the treatment of moderate-to-severe plaque psoriasis in patients who are candidates for systemic therapy.

Systemic therapy includes conventional treatments, (e.g. cyclosporin, methotrexate, fumaric acid esters, acitretin, oral steroids, psoralen ultraviolet A (PUVA)) and biologic treatments (e.g. adalimumab, infliximab, etanercept, and ustekinumab).

1.2 Purpose

Understanding the patient's perspective on their disease and treatment is an important component of clinical research and medical practice. The purpose of this patient centric study is to assess whether patient QoL outcomes are impacted by the exposure to prior treatment prior to starting treatment with secukinumab 300 mg s.c. in relation to the highest skin efficacy response expected at Week 16 and the skin efficacy response at Week 52. Feedback from patients on QoL outcomes will be assessed using a combination of dermatology-related, general health-related and psoriasis-related questionnaires: DLQI [REDACTED] EQ-5D[®] (overall health status); NRS (itching, scaling and pain VAS); HAQ -DI (functional ability and activity restriction - only in patients with concomitant PsA); TSQM (treatment satisfaction) and PBI (treatment benefit). The use of these PROs was discussed and agreed with dermatologist and patient representatives.

[REDACTED]

Finally skin efficacy and QoL will be investigated to generate hypotheses on possible correlations of relevance.

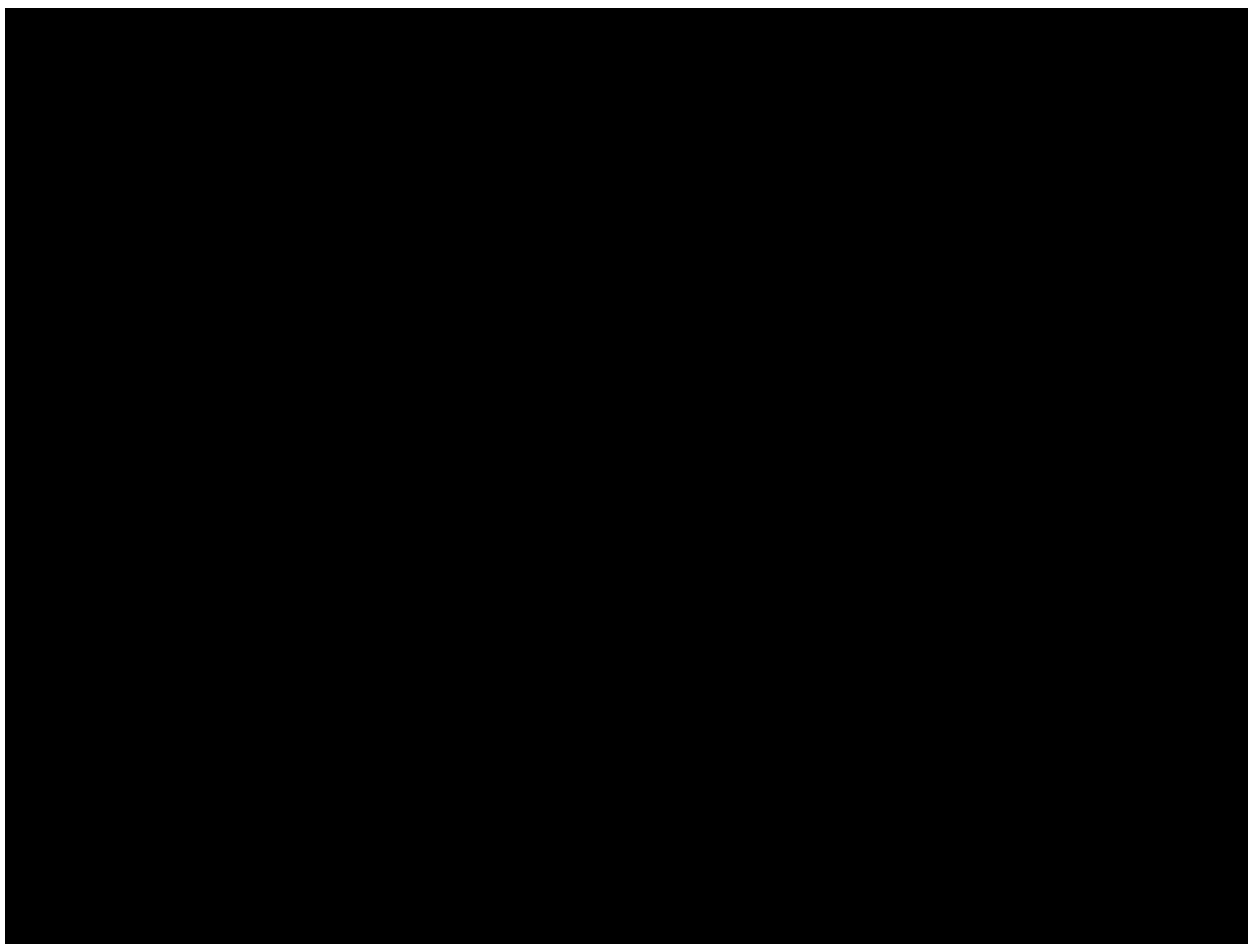
2 Study objectives

2.1 Primary objective

- To assess the proportion of patients achieving a DLQI 0/1 response at Week 16 in 3 pre-defined subpopulations and in the overall study population.
- [REDACTED]

2.2 Secondary objectives

- To assess the proportion of patients achieving a DLQI 0/1 response at Week 52 in 3 pre-defined subpopulations and in the overall study population.
- To assess the effects of treatment with secukinumab 300 mg with respect to changes in EQ-5D[®], HAQ[®]-DI, NRS, TSQM and PBI response over time up to Week 16 and Week 52 compared to Baseline in 3 pre-defined subpopulations and in the overall study population.
- To assess the proportion of patients achieving PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1 responses at Week 16 and Week 52 in 3 pre-defined subpopulations and in the overall study population.
- To assess the proportion of patients with DLQI scores 2-5, 6-10, 11-20, 21-30 at Week 16 and Week 52 compared to Baseline in 3 pre-defined subpopulations and in the overall study population.
- To assess the overall safety and tolerability of treatment with secukinumab 300 mg in 3 pre-defined subpopulations and in the overall study population.



3 Investigational plan

3.1 Study design

The study will utilize an open-label, prospective, non-randomized but stratified multicenter study design. The study will take place across Europe, in approximately 250 study centers in 30 European countries. The study will be implemented in both hospital-based and office-based settings; secukinumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis and whose center fulfills ICH Good Clinical Practice (GCP) quality requirements for the conduct of clinical trials ([CHMP/EWP/2454/02 corr](#)).

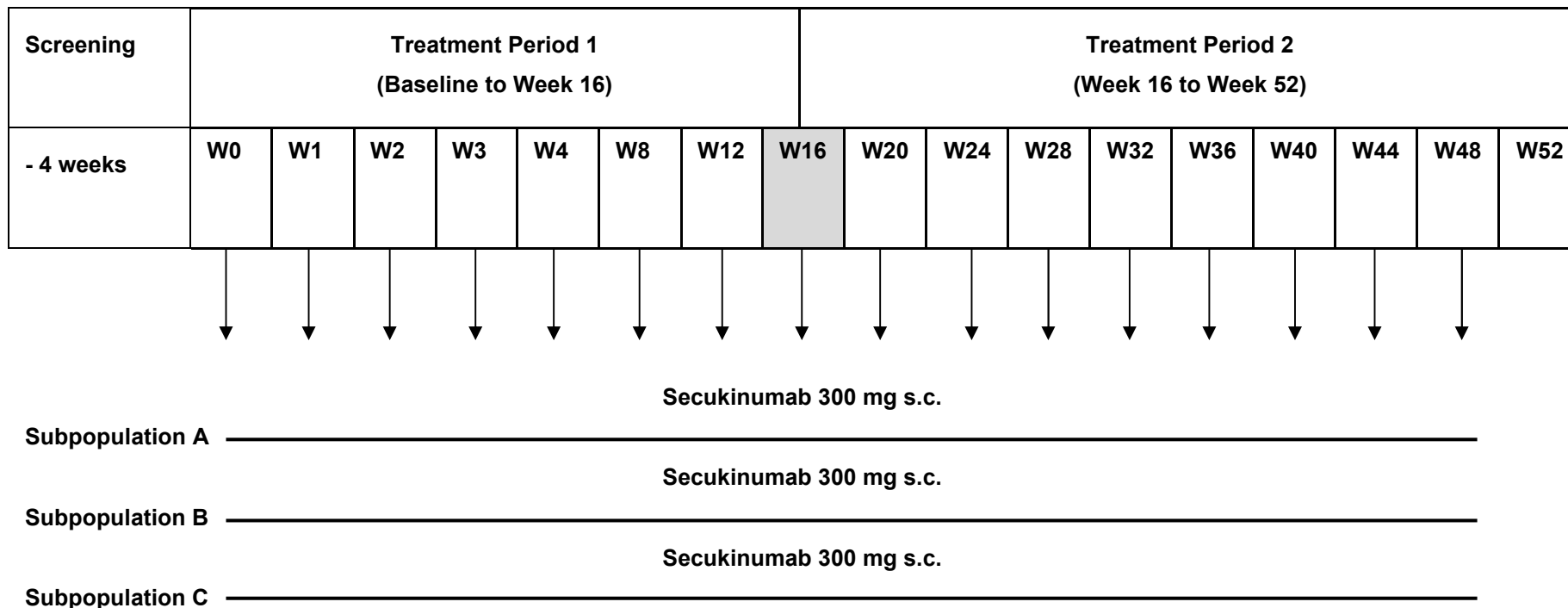
Eligible patients will be categorized at Baseline according to previous exposure to treatment in one of the following 3 subpopulations:

- **Subpopulation A:** Patients who are **naïve to any systemic treatment**, e.g. patients failing or intolerant to previous topical treatment, including narrow band UVB, but never exposed to any systemic treatment, with or without contraindications to the use of conventional systemic treatment and in a need of a first systemic treatment.
- **Subpopulation B:** Patients who have been **previously exposed to at least one conventional systemic therapy**; either because of failure or intolerance to their previous conventional systemic treatment, they are in a need of a first biologic systemic treatment;
- **Subpopulation C:** Patients who have been **previously exposed to at least one biologic systemic therapy**; either because of failure or intolerance to their previous biologic systemic treatment, they are in a need of a different biologic systemic treatment.

All patients are scheduled to receive s.c. injections of secukinumab 300 mg at Week 0, 1, 2 and 3 during the first 4 weeks followed by monthly maintenance dosing of 300 mg secukinumab starting at Week 4 until Week 48. Consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment (e.g. patients who did not achieve a PASI 50 response). If discontinued, patients will complete the end of study visit assessments. Some patients with an initially partial response (e.g. patients who achieve a PASI 50 response but not a PASI 75 response) may subsequently improve with continued treatment beyond 16 weeks.

The primary endpoint is the proportion of patients achieving a DLQI 0/1 response at Week 16 in the 3 pre-defined subpopulations and in the overall study population. The study design is presented in [Figure 3-1](#).

Figure 3-1 Study design

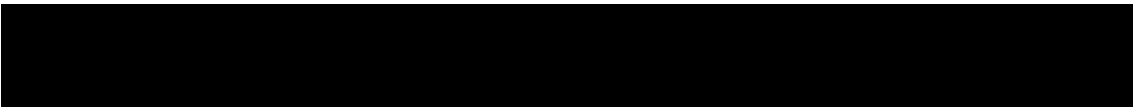


Notes: The primary endpoint will be assessed at Week 16.

Subpopulation A: Patients who are **naïve to any systemic treatment**, e.g. patients failing or intolerant to previous topical treatment, including narrow band UVB, but never exposed to any systemic treatment, with or without contraindications to the use of conventional systemic treatment and in a need of a first systemic treatment.

Subpopulation B: Patients who have been **previously exposed to at least one conventional systemic therapy**; either because of failure or intolerance to their previous conventional systemic treatment, they are in a need of a first biologic systemic treatment;

Subpopulation C: Patients who have been **previously exposed to at least one biologic systemic therapy**; either because of failure or intolerance to their previous biologic systemic treatment, they are in a need of a different biologic systemic treatment.



3.2 Rationale for study design

The pool of eligible patients affected by moderate to severe psoriasis is stratified into 3 subpopulations to study whether a previous exposure to systemic treatments may have an effect on skin efficacy and QoL while on treatment with the same regimen of secukinumab 300 mg as per the EU SmPC. Therefore, there is neither the need for blinding the study treatment nor to randomize the patients. In addition, the interest in this study is to assess how

The inclusion of homogeneous subpopulations is needed in order to ensure sufficient power to detect clinically relevant outcomes in each category.

The primary endpoint of this trial will be assessed at Week 16. This time point was chosen because the plateau of efficacy of treatment with secukinumab 300 mg was reached at 16 weeks in the Phase 3 trials (see Section 1). A correlation between the PASI response and the DLQI response at Week 12 was already observed in the Phase 3 trials and it is also expected to be observed at Week 16 (DLQI response was not collected at Week 16 in the Phase 3 placebo-controlled trials).

Secukinumab will be used according to the posology described in the EU SmPC. The recommended dose is 300 mg of secukinumab by subcutaneous (s.c.) injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as 2 s.c. injections of 150 mg. Consideration will be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.

According to the EU S3 Guidelines on the systemic treatment of psoriasis vulgaris, the drugs that produce the highest PASI reduction by the end of induction therapy are also associated with the greatest reduction in DLQI (Katugampola et al 2007, Pathirana et al 2009).

Furthermore, as the study design provides for a total treatment duration of 52 weeks, it also allows for the long-term assessment of the impact of the exposure to a previous treatment prior to start of treatment with secukinumab 300 mg s.c. on QoL outcomes and is aligned with the duration of the core Phase 3 trials.

Secukinumab was approved in the EU for the treatment of moderate-to-severe plaque psoriasis in patients who are candidates for systemic therapy.

Systemic therapy includes conventional treatments, (e.g. cyclosporin, methotrexate, fumaric acid esters, acitretin, oral steroids, PUVA) and biologic treatments (e.g. adalimumab, infliximab, etanercept, and ustekinumab). Hence, candidates for systemic therapy may be divided into 3 different patient subpopulations:

- **Subpopulation A:** Patients who are **naïve to any systemic treatment**, e.g. patients failing or intolerant to previous topical treatment, including narrow band ultraviolet B (UVB) but never exposed to any systemic treatment, with or without contraindications to the use of conventional systemic treatment and in need of a first systemic treatment.

- **Subpopulation B:** Patients who have been **previously exposed to at least one conventional systemic therapy**; either because of failure or intolerance to their previous conventional systemic treatment, they are in need of first biologic systemic treatment.
- **Subpopulation C:** Patients who have been **previously exposed to at least one biologic systemic therapy**; either because of failure or intolerance to their previous biologic systemic treatment, they are in need of a different biologic systemic treatment.

Feedback from patients on their QoL outcomes will be assessed using a combination of dermatology-related, general health-related and psoriasis-related questionnaires: DLQI [REDACTED]; EQ-5D[®] (overall health status); NRS (itching, scaling and pain VAS); HAQ -DI (functional ability and activity restriction - only in patients with concomitant PsA); TSQM (treatment satisfaction) and PBI (treatment benefit). The selection of these PROs was discussed and agreed with dermatologist and patient representatives in order to provide meaningful data to characterize the patients' perspective while keeping a reasonable burden on responders to questionnaires.

Rationale for conducting an interventional study

An interventional study is required to introduce high quality standardizations for the trial conduct and to mitigate risks for data variability that could compromise the subsequent data analysis:

- A mandatory treatment regimen of secukinumab 300 mg s.c. as per the EU SmPC streamlines possible differences in the approved prescribing information of participating European countries.
- Local medical assessment practices are also streamlined with regard to rules and processes for captured study outcomes and concomitant use of psoriasis medication (e.g. topical treatments).
- It is necessary to harmonize the wash-out period for other systemic anti-psoriasis therapies prior to the start of the study to ensure robust data.
- ICH GCP E6 guideline adherence during study conduct enables the collection of high quality data (e.g. completeness and correctness of data).

Rationale for selection of patient reported outcomes

The EQ-5D[®] assesses each subject's overall health status and is a standardized tool for use as measure of health outcome. It has been extensively used in several dermatological conditions including psoriasis (Rønneberg Mehren et al 2014). It consists of a descriptive system of 5 symptom domains, each with 3 response levels (no problems, some problems, severe problems), and the EQ-5D[®] VAS from 0 (worst possible health state) to 100 (best possible health state), both of which are completed by the subject. The EQ-5D[®] minimal important difference in psoriasis patients with body surface area (BSA) >5% is in the range of 3.82-8.43 (Shikiar et al 2006). The tool was used during the Phase 3 clinical program for secukinumab. Large improvements from Baseline were seen in the pain/discomfort domain, including extreme pain, and in the anxiety/depression domain for secukinumab compared to placebo and gains in overall health status from Baseline were seen versus placebo and etanercept at Week 12 (Study CAIN457A2302: +19.5 and +16.9 for 300 mg and 150 mg doses, -0.7 for

placebo; Study CAIN457A2303: +22.3 and +19.7 for 300 mg and 150 mg doses, +14.4 for etanercept, +2.2 for placebo).

The Dermatology Life Quality Index (DLQI) developed in 1994 (Finlay and Khan 1994), was the first dermatology-specific QoL instrument. Widely used (tested across >40 different skin conditions and available in >90 languages, Basra et al 2008), it is a self-administered assessment of 6 domains: daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school over the previous one week. DLQI total scores range from 0 to 30 (sum of 10 questions, each ranging from 0 (not at all) to 3 (very much)) with higher scores indicating greater impairment in health-related QoL (HR-QoL). Several studies demonstrated a good correlation between the reduction in PASI score and the reduction in DLQI (Vender et al 2012, Driessen et al 2010).

In a meta-analysis including randomized controlled trials of biological agents for the treatment of moderate-to-severe psoriasis, the authors highlighted how the achievement of a better DLQI response was greater in patients with >75% mean PASI reduction compared to those achieving a mean PASI reduction of 50–75% or below (Mattei et al 2014). Although PASI 75 is considered a meaningful cut-off, the European Medicines Agency (EMA) Guidelines (CHMP/EWP/2454/02 corr) define treatment success on the basis of at least 90% improvement in PASI from Baseline. While the additional QoL benefit of achieving mean PASI reductions of 90% is intuitive, it still needs to be demonstrated.

Results from the secukinumab Phase 3 program have shown that a large proportion of patients suffering from moderate to severe plaque psoriasis were able to achieve PASI 90 response at 16 weeks, when treated with 300 mg s.c. (PASI 90 response rate up to 70%). The response rate was maintained up to Week 52 (PASI 90 response rate of 63%). In addition, 81.8% of patients with cleared or almost cleared skin at Week 24 maintained clear skin at Week 52 (Callis et al 2014, Rich et al 2013, Sigurgeirsson et al 2014, Paul et al 2014). In Study CAIN457A2303, secukinumab showed clear superiority over etanercept in both primary (PASI 75 and IGA 0/1) and secondary endpoints including the DLQI 0/1 assessment. Furthermore, an early onset of efficacy, based on 50% improvement in PASI scores was observed at Week 3 with secukinumab 300 mg s.c. compared to Week 8 with etanercept (Blauvelt et al 2015).

The Minimal Clinically Important Difference (MCID) of the DLQI in inflammatory skin diseases has been estimated in 5 studies in the range of 2.2-6.9 points (Langley et al 2014). In patients with psoriasis and on biologic therapy, a ≥ 5 -point reduction in total DLQI score is considered the MCID (Augustin et al 2011). Mean decreases (improvements) in DLQI from Baseline were -11.5 and -10.1 for the secukinumab 300 mg and 150 mg doses versus -1.1 for placebo ($p < 0.0001$ for each dose versus placebo) in Study CAIN457A2302 at Week 12 and -10.4 and -9.7 for secukinumab 300 mg and 150 mg, respectively, versus -7.9 for etanercept and -1.9 for placebo in Study CAIN457A2303 ($p < 0.0001$ for each dose versus either placebo or etanercept) at Week 12. Thus secukinumab demonstrated clinically meaningful improvements in DLQI score in both large studies, but whether a previous psoriasis treatment may impact on DLQI scoring has not yet deeply investigated.



[REDACTED]

In a large, multinational, population-based survey of psoriasis and/or PsA in North America and Europe patients indicated that their most bothersome signs or symptoms were itching (43%) and scaling (23%) (Lebwohl et al 2014). The NRS is an 11-point VAS used to evaluate the patient assessment of their main skin symptoms and signs such as itching, scaling and pain.

Since psoriasis is an immune-mediated, chronic inflammatory disease, it may also result in systemic pathological effects. The severe forms have been associated with several diseases that have similar pathogenic factors. Psoriatic arthritis is a comorbidity classically associated with psoriasis (Moll et al 1973, Gladman 2004, Gladman et al 2005, Ibrahim et al 2009). The HAQ[®]-DI assesses the long term influence of chronic disease on functional ability and activity restriction in patients with a history of PsA (Fries et al 1982). The HAQ[®]-DI score can range from 0 to 3, with 0 indicating no disease, and 3 indicating worst possible disease. A change in score of 0.3 is usually considered clinically meaningful. The mean decrease (improvement) in HAQ[®]-DI from Baseline was greatest for the secukinumab 300 mg group at 12 weeks (-0.38 and -0.18 for 300 mg and 150 mg secukinumab vs. -0.04 for placebo) and was sustained at 52 weeks (-0.39 and -0.20 for 300 mg and 150 mg secukinumab). For the 300 mg dose, these results are clinically important (i.e. beyond the MCID) in this comorbid population and favor the 300 mg secukinumab dose. Eighteen percent of patients in the Phase 3 program reported concomitant PsA at Baseline hence confirmation from a large study would be important.

Treatment success is highly influenced by patient satisfaction, as demonstrated by several studies investigating treatment satisfaction in psoriatic patients treated with biologics. Although satisfaction with treatment was generally high, room for improvement was constantly detected in the “effectiveness” domain, which included the rapidity of onset of the clinical improvement in the “side-effects” and “convenience” domains of the TSQM (van Cranenburgh et al 2013, van den Reek et al 2014).

The PBI is another tool developed to assess patient relevant benefits in the treatment of psoriasis: before treatment, the patient is asked about those benefits of treatment that are personally important to him/her; during or after treatment, the extent to which these patient-defined aims of treatment are being/were achieved is recorded (Feuerhahn et al 2012). Both PROs, TSQM and PBI, were not assessed during the Phase 3 clinical program of secukinumab.

Rationale for selection of factors potentially impacting on skin efficacy and QoL outcomes

Compared to PsA, other comorbidities have been described as associated with psoriasis, including the metabolic syndrome as an independent risk factor for death and its individual components, which include arterial hypertension, adiposity and abnormalities in lipid and glucose metabolism (Henseler et al 1995, Christophers 2007, Naldi et al 2010, Augustin et al 2010). This association is believed to account, at least partially, for the higher rate of cardiovascular complications observed among patients with psoriasis and contribute to the decreased life expectancy observed in patients with severe disease. Treatment of psoriasis has

[REDACTED]

the potential to significantly improve patient outcomes and possibly also protect against comorbidities (Reich 2012).

The burden of the physical and psychological comorbidities and stigma associated with psoriasis and the external factors and coping strategies modulated by the patient's personality accumulated over the course of their lives may induce a progressive impairment in these patients, hence the duration of the disease is another important factor potentially impacting on the QoL (Ros et al 2014).

Several studies have demonstrated that plaques localization on visible body parts (legs, arms, and head) had a greater impact on the QoL than lesions located on other areas (Finlay and Coles 1995, O'Neill and Kelly 1996). It is also very likely that cosmetic disfigurement and itch may contribute to determining the burden of the illness (Touw et al 2001). For etanercept and adalimumab, data from post hoc analyses were published that suggested a similar sequential change in psoriasis symptom patterns in different body regions for treatment responders. Skin symptom improvements started from the head and trunk region in particular with improvement in desquamation and induration. Resolution of erythema and improvement in plaques in the body region extremities, especially the lower extremities, were observed later (Griffiths et al 2015, Navarini et al 2012). A prospectively planned exploration on the dynamics of psoriasis symptom patterns once secukinumab treatment has started can deepen the understanding of symptom progress to better manage expectations of patients in daily medical practice.

Concomitant psoriasis treatments are very common in the management of moderate to severe psoriasis, with the aim to optimize the systemic treatment effect on the skin or when comorbidities are associated e.g. PsA (Heydendael et al 2004, Paul et al 2011). Examples of these co-medications are topical steroids, PUVA, emollients or a combination of these. Their concomitant use with a biologic treatment could have a significant impact on patient QoL and satisfaction (Albrecht et al 2011).

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

The efficacy and safety of secukinumab 300 mg s.c. for the treatment of moderate-to-severe plaque psoriasis has been demonstrated in the Phase 3 clinical program as described in Section 1. The 300 mg s.c. dose of secukinumab consistently delivered the most clinically meaningful benefit to patients compared to the 150 mg s.c. dose across all pivotal studies for all time points (Week 12 to Week 52) and the best risk/benefit profile as the safety profile of the 300 mg dose did not significantly differ from that of the 150 mg dose in the clinical program.

Pre-filled syringes (PFS) have been selected for secukinumab s.c. administration in this study as these have been successfully used by patients in the Phase 3 clinical trials (Blauvelt et al 2015, Langley et al 2014), which showed the use of PFS was safe and well tolerated. Self-injection with the PFS, following the utilized instructions for use (IFU), showed no significant safety hazards and was found to be acceptable to study participants and to the competent authorities for other secukinumab studies (CAIN457A2312, CAIN4572313 and CAIN457A3301). Use of PFSs was approved by the EMA.

Based on the results from the pivotal secukinumab Phase 3 studies in moderate to severe plaque psoriasis (CAIN457A2302 and CAIN457A2303), the plateau of efficacy was observed around Week 16; therefore, Week 16 has been selected as the time point for the core study, as described in [Section 3.2](#).

A second treatment period will follow for an additional 36 weeks, bringing the total treatment period to 52 weeks, to provide continued treatment for patients who respond to treatment between Baseline and Week 16 (e.g. patients who achieved a PASI 75 response) and for patients who have an initial partial response to treatment between Baseline and Week 16 (e.g. patients who achieved a PASI 50 response but not a PASI 75 response; consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment). The total treatment duration of 52 weeks is aligned with the treatment duration of the Phase 3 clinical studies.

Phase 3 studies in the secukinumab clinical program included a 12-week follow-up period, deemed necessary to evaluate the safety of secukinumab after the last dose administration. Considering that in this study the posology used is the one approved in the EU [SmPC](#) and no new safety signals are expected ([Blauvelt et al 2015](#)) such treatment free follow-up is not deemed necessary in this study protocol.

3.4 Rationale for choice of comparator

This study is designed primarily to assess whether the improvement of QoL, measured by the proportion of patients achieving a DLQI 0/1 response in patients with moderate to severe plaque psoriasis treated with secukinumab 300 mg s.c. varies within 3 subpopulations of patients naïve to or previously exposed to systemic treatments for psoriasis. Therefore, no placebo or other comparator treatment will be included in the study.

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis describing the self-reported Baseline characteristics and HR-QoL of patients prior to treatment may be performed for this study after last patient, first treatment (LPFT). Details will be described in the Statistical Analysis Plan (SAP).

3.6 Risks and benefits

Secukinumab has shown confirmed efficacy in psoriasis and preliminary efficacy in several inflammatory diseases, e.g. rheumatoid arthritis, ankylosing spondylitis, PsA: up to 12 000 patients have been enrolled in studies with secukinumab with over 9 600 having received active drug at doses ranging from single and/or multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25 mg to 300 mg s.c. An extensive Phase 2/3 program (conducted in 4 546 patients, 3 430 of those treated with secukinumab) demonstrated secukinumab to be very effective in treating plaque psoriasis, with 300 mg being the dose that delivered the highest benefit to patients with respect to achievement of almost clear to clear skin, improved QoL, speed of onset of action, and sustainability of symptom relief. From a safety perspective, secukinumab was overall well tolerated.

Secukinumab has the potential to increase the risk of infections. In clinical studies, infections have been observed in patients receiving secukinumab. Most of these were mild or moderate

upper respiratory tract infections such as nasopharyngitis and did not require treatment discontinuation. Related to the mechanism of action of secukinumab, non-serious mucocutaneous *Candida* infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies (3.55 per 100 patient years for secukinumab 300 mg versus 1.00 per 100 patient years for placebo). Caution should be exercised when considering the use of secukinumab in patients with a chronic infection or a history of recurrent infection, and exclusion criteria are applied in this study to minimize the risk (Section 4.2). Patients will be instructed to seek medical advice if signs or symptoms suggestive of an infection occur.

If a patient develops a serious infection, the patient will be closely monitored and secukinumab should not be administered until the infection resolves. No increased susceptibility to tuberculosis was reported from clinical studies. However, secukinumab should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of secukinumab in patients with latent tuberculosis. Exclusion criteria are applied in this study to minimize the risk (Section 4.2) and additional guidance is provided in Section 6.2.7.

Caution should be exercised when treating with secukinumab patients with Crohn's disease as exacerbations of Crohn's disease, in some cases serious, were observed in clinical studies in both secukinumab and placebo groups. Patients who are treated with secukinumab and have Crohn's disease will be eligible but will be followed closely.

If an anaphylactic or other serious allergic reaction occurs, administration of secukinumab should be discontinued immediately and appropriate therapy initiated.

The removable needle cap of the PFS contains a derivative of natural rubber latex. No natural rubber latex has to date been detected in the removable needle cap. Nevertheless, the use of secukinumab PFS in latex-sensitive individuals has not been studied and there is therefore a potential risk of hypersensitivity reactions, which cannot be completely ruled out. Exclusion criteria are applied in this study to minimize the risk (Section 4.2).

Live vaccines should not be given concurrently with secukinumab. Patients receiving secukinumab may receive concurrent inactivated or non-live vaccinations. In a study, after *meningococcal* and inactivated influenza vaccinations, a similar proportion of healthy volunteers treated with 150 mg of secukinumab and those treated with placebo were able to achieve an adequate immune response of at least a 4-fold increase in antibody titers to *meningococcal* and influenza vaccines. The data suggest that secukinumab does not suppress the humoral immune response to the *meningococcal* or influenza vaccines. Exclusion criteria are applied in this study to minimize the risk (Section 4.2).

Most of the experience to date has been with secukinumab s.c. doses up to 300 mg and i.v. doses up to 10 mg/kg; there are limited data at this time for higher doses. No cases of overdose have been reported for secukinumab. Single doses of secukinumab up to 30 mg/kg (i.e. approximately 2 000 to 3 000 mg) have been administered i.v. in clinical studies in other autoimmune indications, and doses up to 3×10 mg/kg i.v. have been administered in psoriasis studies without acute dose-limiting toxicity.

Adverse events (AEs)/serious adverse events (SAEs) occurring during clinical trials with secukinumab should be managed based on the best clinical judgment of the Investigator in the context of the underlying disease and treated as clinically warranted.

Novartis standard processes aligned with international guidelines apply for the reporting of safety events.

Secukinumab 300 mg was approved in EU in January 2015 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy on the basis of the Phase 2/3 program data. This Phase 4 study will be conducted in compliance with the requirements of **Section 4.4, Warnings and Precautions** of the EU [SmPC](#)).

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

Further details are provided in the EU [SmPC](#) and in the Investigator's Brochure (IB) for secukinumab.

4 Population

The study population will consist of a representative group of male and female patients (≥ 18 years old) with moderate to severe plaque-type psoriasis. Moderate to severe plaque-type psoriasis is defined for this study by taking into consideration the European Psoriasis guideline ([CHMP/EWP/2454/02 2004 corr](#)), the published European Consensus ([Mrowietz et al 2011](#)) and the definition used in the Phase 3 clinical program. Hence, moderate to severe plaque-type psoriasis is defined by a total PASI score of ≥ 10 , an IGA mod 2011 score ≥ 3 and a BSA $\geq 10\%$. Prior to entering the study, patients may either be naïve to systemic treatment (with or without contraindications to conventional systemic treatments) or have previously been exposed to at least one systemic therapy (conventional or biologic) to treat their psoriasis.

4.1 Inclusion criteria

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

1. Patients must be able to understand and communicate with the Investigator and comply with the requirements of the study (including administration of s.c. injections at home) and must provide 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 aged at least 18 years at time of Screening.
3. Moderate to severe plaque-type psoriasis diagnosed for at least 3 months prior to Screening and candidate for systemic therapy.

Moderate to severe plaque-type psoriasis is defined at Baseline by:

- PASI score ≥ 10 and
- IGA mod 2011 score ≥ 3 and
- BSA $\geq 10\%$

Candidate for systemic therapy is defined as a patient having moderate to severe plaque-type psoriasis that is inadequately controlled by:

- Topical treatment (patients who were naïve to systemic treatments).

- Phototherapy and/or previous systemic therapy (either conventional or biologic systemic therapy).

4.2 Exclusion criteria

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

The exclusion criteria are compliant with the information reported in the EU secukinumab PFS SmPC; however, additional criteria are used or additional details provided due to the study context (e.g. to allow appropriate assessment of efficacy or safety in accordance with ICH GCP requirements).

1. Forms of psoriasis other than moderate to severe plaque-type psoriasis, e.g. drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium) at Screening.
2. Patients with previous treatment with any agent targeting interleukin (IL)-17 directly or IL-17 receptor A (e.g. secukinumab, ixekizumab, or brodalumab).
3. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (> 5 mIU/mL).
4. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant unless they use effective contraception during the entire study or longer if required by locally approved prescribing information (e.g. 20 weeks in EU). Barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide (where available). Note: spermicides alone are not a barrier method of contraception and should not be used alone. The following methods are considered more effective than the barrier method and are also acceptable:
 - Total abstinence: When this is in line with the preferred and usual lifestyle of the patient (periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception).
 - Female sterilization: have had a surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
 - Male partner sterilization at least 6 months prior to Screening. For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
 - Use of established oral, injected or implanted hormonal methods of contraception, intrauterine device or intrauterine system post-ovulation methods).

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

- 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or
 - 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [for US only: and estradiol < 20 pg/mL] or
 - Surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.
5. Active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of secukinumab therapy.
 6. Underlying condition (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 patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy. Patients who are treated with secukinumab and have Crohn's disease are eligible but should be followed closely.
 7. Investigator discretion should be used for patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders.
 8. Significant medical problems including but not limited to the following: uncontrolled hypertension (systolic ≥ 160 mmHg and/or diastolic ≥ 95 mmHg), congestive heart failure (New York Heart Association (NYHA) status of class III or IV).
 9. Patients with a serum creatinine level exceeding 176.8 $\mu\text{mol/L}$ (2.0 mg/dL).
 10. Screening total white blood cell (WBC) count < 2 500/ μL , or platelets < 100 000/ μL or neutrophils < 1 500/ μL or hemoglobin < 8.5 g/dL.
 11. Active systemic infections during the last 2 weeks (exception: common cold) prior to Baseline and any infections that reoccur on a regular basis; Investigator discretion should be used regarding patients who have travelled or resided in areas of endemic mycoses, such as histoplasmosis, coccidioidomycosis or blastomycosis and for patients with underlying conditions that may predispose them to infection, such as advanced or poorly controlled diabetes.
 12. History of an ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by a positive or indeterminate QuantiFERON TB-Gold test (QFT) at Screening. Patients with a positive or indeterminate QFT test may participate in the study if a full tuberculosis (TB) work-up (according to local practice/guidelines) completed within 12 weeks prior to Day 1 (Baseline) establishes conclusively that the patient has no evidence of active TB. If presence of latent TB is established then treatment must have been initiated and maintained according to local country guidelines prior to Day 1 (Baseline).
 13. Past medical history record of, or current infection with, human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus prior to Baseline.
 14. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for Bowen's disease of the skin, or basal cell carcinoma or actinic keratosis that have been treated with no

- evidence of recurrence in the past 12 weeks; carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed).
15. Current severe progressive or uncontrolled disease, which in the judgment of the clinical Investigator renders the patient unsuitable for the study or puts the patient at increased risk (e.g. myocardial infarction within 26 weeks prior to Baseline).
 16. Inability or unwillingness to undergo repeated venipuncture (e.g. because of poor tolerability or lack of access to veins) or self-injection with the PFS.
 17. Patients who are allergic to rubber or latex or with history of hypersensitivity reactions to any of the excipients.
 18. 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.
 19. History or evidence of ongoing alcohol or drug abuse within the last 6 months before Baseline.
 20. Plan for administration of live vaccines during the study period or 6 weeks prior to Baseline.
 21. Use of investigational treatment within 4 weeks before Baseline, or within a period of 5 half-lives of the investigational treatment, whichever is longer.
 22. Patients not willing to limit UV light exposure (e.g. sunbathing and/or the use of tanning devices) during the course of the study.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The same investigational treatment will be given to all patients recruited in the 3 subpopulations: secukinumab/AIN457 300 mg s.c. as per EU-approved [SmPC](#). No reference therapy will be given.

Secukinumab for s.c. injection will be supplied in single boxes each containing prefilled syringes (PFS) of 150 mg secukinumab in a 1 mL liquid formulation. The study drug supplies will be open label. Secukinumab 300 mg (2 × PFS of the 150 mg dose) will be self-administered by the patient at Baseline, Weeks 1, 2, 3, 4, 8, and 12 during Treatment Period 1 and at Week 16, 20, 24, 28, 32, 36, 40, 44 and 48 during Treatment Period 2.

Patients will receive instructions and training from study center staff on how to use and self-administer the study drug. The injections up to Week 16 and the subsequent ones occurring during a visit will be performed by the patient (or caregiver) at the study center, under the supervision of the investigational site staff. The injections not occurring during a study center visit will be performed by the patient (or caregiver) at their home.

5.1.2 Additional treatment

No additional treatment other than the investigational drug will be provided for this study.

5.2 Treatment subpopulations

Eligible patients will be stratified at Baseline according to previous exposure to treatment in 3 subpopulations:

- **Subpopulation A:** 646 patients who are **naïve to any systemic treatment**, e.g. patients failing or intolerant to previous topical treatment, including narrow band ultraviolet B (UVB) but never exposed to any systemic treatment, with or without contraindications to the use of conventional systemic treatment and in need of a first systemic treatment.
- **Subpopulation B:** 646 patients who have been **previously exposed to at least one conventional systemic therapy**; either because of failure or intolerance to their previous conventional systemic treatment, they are in need of first biologic systemic treatment.
- **Subpopulation C:** 323 patients who have been **previously exposed to at least one biologic systemic therapy**; either because of failure or intolerance to their previous biologic systemic treatment, they are in need of a different biologic systemic treatment.

All patients will be assigned to receive the same treatment regimen:

- **Secukinumab 300 mg regimen:** Secukinumab 300 mg s.c. (supplied in single boxes each containing 2 × PFS of the 150 mg dose for s.c. injection) self-administered at Baseline, once weekly at Week 1, 2 and 3, and thereafter at 4-weekly intervals starting Week 4 until Week 48 inclusive.

The treatment administration schedule is presented in [Table 5-1](#) and the treatment administration schedule is presented in [Table 6-2](#).

Table 5-1 Overview of treatment during the study

Treatment Period 1 (Baseline to Week 16)	
(Self-administration at Study Center)	(Self-administration at Home)
Baseline & Weeks 1, 2, 3, 4, 8, and 12	None
Treatment Period 2 (Week 16 to Week 52)	
(Self-administration at Study Center)	(Self-administration at Home)
Week 16, 20, 24, 36 and 48	Week 28, 32, 40 and 44

5.3 Treatment assignment and randomization

This is a non-randomized, single regimen study. At the Screening Visit, every patient will be registered in an electronic study system. The Investigator or his/her delegate will check that the patient fulfills all the inclusion/exclusion criteria before assigning study drug to the patient.

At Baseline, eligible patients will be stratified according to previous exposure to treatment in 3 subpopulations as described above ([Section 5.2](#)).

To ensure that recruitment of patients fulfills the required sample size for each of the subpopulations the electronic study system will indicate the stop of the allocation to a



subpopulation when the planned number of patients is achieved in the respective subpopulation.

5.4 Treatment blinding

This is an open-label, single regimen study; the study drug will not be blinded.

5.5 Treating the patient

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

5.5.1 Patient numbering

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

Upon signing the informed consent form (ICF), the patient is assigned the next sequential number by the Investigator. The Investigator or his/her staff will contact the electronic study system and provide the requested identifying information for the patient to register them into the study. The study center should select the case report form (CRF) book with a matching Patient Number from the data capture system to enter data.

If the patient fails to be treated for any reason, the electronic study system must be notified that the patient was not treated. The reason for not being treated will be entered in the CRF.

5.5.2 Dispensing the study drug

Each study site will be supplied by Novartis with study drug in packaging of similar appearance depending on the commercial availability of the study drug. The study drug packaging has either a 2-part label or commercially available drug will be used following local requirements. Investigator staff will select the study drug to dispense to the patient after successful registration of the patient in the electronic study system. If applicable, immediately before dispensing study drug to the patient, Investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique Patient Number or drug accountability records for the commercially available kits must be completed to allow traceability.

From Week 28, once the home study drug administration applies, patients will be expected to perform home drug administrations at the protocol specified time-points. For these cases, the Investigator will dispense, supported by the electronic study system, an appropriate number of investigational treatment packages for home administrations. The patients will record details including the date of administration at home in a self-administration log and will return the used medication (if in compliance with local rules and guidelines) and medication packaging, together with the self-administration log, at their next visit to the study center. Patients will be asked to return all unused study drug and packaging at each scheduled study visit and by the very latest at the end of the study.



5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

The study drug must be received by appropriate personnel at the study center, handled and stored safely and properly, and kept in a secured location to which only appropriate study personnel have access. Upon receipt, all study drugs should be stored according to the local process instructions. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported as per Novartis processes.

The PFS sealed in their outer box must be stored in a locked refrigerator between 2°C and 8°C (36°F and 46°F) and must be carefully controlled in accordance with regulations governing investigational medicinal products, local regulations and in accordance with instructions from the Novartis Drug Supply Management or Novartis Drug Supply Chain or corresponding service providers. The study drug should be protected from the light and must not be frozen.

Study drug labels, if applicable, will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study drug including the study drug number.

The Pharmacist, Investigator, or other qualified study center personnel must maintain an accurate record of the shipment and dispensing of the study drug. Monitoring of drug accountability will be performed by the field monitor continuously during study center visits and finally reconciled at the completion of the study.

Patients will be asked to return all used study drug (if possible according to local guidelines and practice), unused study drug and packaging at the following visit but latest at the end of the study or at the time of discontinuation of study drug.

At the conclusion of the study, and as appropriate during the course of the study, study drug documentation will be archived by site personnel and by the Novartis monitor or similar study function as per Novartis processes.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Patients will self-administer secukinumab by s.c. injection using a PFS. Each 300 mg dose will consist of 2 × 150 mg s.c. injections of 1 mL each. The dosing frequency will be either weekly or every 4 weeks in accordance with the administration schedule ([Table 5-1](#) and [Table 6-2](#)). The last dose administration will occur at Week 48.

Patients will receive instructions and training from study center staff on how to self-administer the study drug. The injections up to Week 16 and the subsequent ones occurring during a visit will be done by the patient (or caregiver) at the study center, under the supervision of the Investigator or study staff (at Baseline, Weeks 1, 2, 3, 4, 8, and 12 during Treatment Period 1; and Week 16, 20, 24, 36 and 48 during Treatment Period 2).

The patient will be instructed on the use of secukinumab via review of IFU for secukinumab PFS (PFS-IFU). At subsequent visits, the Investigator/qualified study center staff will observe

the self-administration of secukinumab at the clinic. The injections not occurring during a study center visit will be done by eligible patients (or caregiver) at their home (Weeks 28, 32, 40 and 44) during Treatment Period 2.

All dosages prescribed and dispensed to the patient during the study must be recorded in the eCRF.

The patient will document all doses, dates and times of self-administration at home in a self-administration log. Patients are required to return the self-administration log at every visit to the study center.

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

At the beginning of the study, the Investigator/qualified study center staff will determine if self-administration is appropriate for the patient, e.g. manual dexterity, ability to follow the secukinumab PFS-IFU. If a patient requires a caregiver to administer study drug, the caregiver should be trained by the Investigator/qualified study center staff. If a caregiver is not available at a particular visit or the patient is having problems with self-administration, the Investigator/qualified study center staff may administer the study drug to the patient. However, all patients should be trained sufficiently and be comfortable with the study drug self-administration before the first home administration visit. Patients should be instructed to contact the Investigator site staff in case of any issue during study drug home administration.

Records of study drug kits assigned to the patient during the study must be documented.

At each visit, all study assessments, including the completion of PROs, should be completed prior to self-injection of the study drug.

5.5.5 Permitted dose adjustments and interruptions of study treatment

In general, treatment interruptions are not permitted. No dose adjustment of study drug is permitted and no interruption of the study drug should be planned during the study, with the following exceptions.

For patients who are unable to tolerate the protocol-specified dosing scheme, dose interruptions of study drug are permitted in order to keep the patient on study drug. The following guidelines should be followed:

- Study drug interruption is permitted if, in the opinion of the Investigator, a patient is deemed to be placed at a safety risk unless dosing is temporarily interrupted. In such cases study drug should be interrupted only during the time that this risk is present and ongoing. Study drug can be started again at the next scheduled visit after resolution of the safety risk.
- The effect of secukinumab on live vaccines is unknown; therefore, live vaccines should not be administered during participation in the study. If the patient received a live virus vaccination during the study, the patient must discontinue study drug and complete the end-of-study visit.

If a dose of secukinumab was dispensed by the electronic study system but not administered to a patient, this deviation event must be recorded in the CRF.

5.5.6 Rescue medication

Rescue medication is not permitted in this study.

As per the EU-approved [SmPC](#), consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 16 weeks.

5.5.7 Concomitant medication

All treatments administered during the 6 months prior to start of study drug (including any treatments started during the Screening period) for any reason NOT including psoriasis will be entered in the eCRF. The start date, end date, dose, unit, frequency, route and reason for administration should be recorded.

In addition, psoriasis treatments used from the time the patient started psoriasis treatment will be reported in the eCRF. All topical treatments, systemic treatments and phototherapies for psoriasis administered will be entered in the eCRF ([Section 6.2.2](#)).

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

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

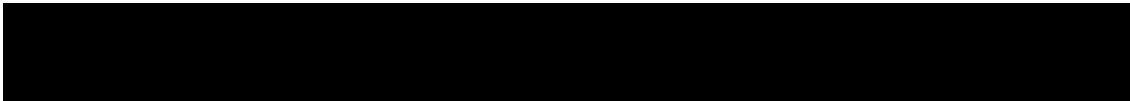
Concomitant medications are allowed if not listed in [Table 5-2](#). Dose adjustments of these medications should be avoided during the study. If a dose adjustment of these medications does occur, it must be recorded on the appropriate eCRF page. There is no restriction on the use of topical corticosteroids (TCS) different from treatment of psoriasis but their use must be recorded under the Concomitant Medications eCRF.

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

5.5.7.2 Permitted concomitant medications for psoriasis

After the Screening period, the use of concomitant emollients (not supplied by Novartis) or other non-medicated interventions (not listed in [Table 5-2](#)) for psoriasis affecting all body regions is allowed. Use of emollients must be recorded on the concomitant medications eCRF. Use of any other non-medicated interventions must also be recorded in the eCRF.

Use of emollients is recommended as a first line intervention but TCS are allowed as a second line intervention for the treatment of plaques at the discretion of the Investigator during the treatment periods. Use of mild potent TCS for limited periods (e.g. up to 7 consecutive days)



is recommended as the first step whilst use of moderate to potent TCS should be considered as the last step, at the discretion of the Investigator. Use of these TCS therapies will be recorded on appropriate eCRF pages including the reason for usage.

5.5.7.3 Permitted concomitant medications for psoriatic arthritis

The use of non-steroidal anti-inflammatory drugs, analgesics or any other medications used to treat PsA will be permitted only if not listed in [Table 5-2](#). Use of these medications must be recorded on the appropriate eCRF page.

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

5.5.8 Prohibited medication

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

The Investigator/qualified study center staff must instruct the patient to notify them about any new treatments the patient takes after the start of the study drug. All prohibited medications and significant non-drug therapies administered after the patient starts study drug must be recorded in the eCRF.

If a prohibited medication listed in [Table 5-2](#) is used during the study, the patient must discontinue use of the prohibited medication if he/she wishes to continue in the study. At the discretion of the Investigator/qualified study center staff, if the patient's use of a prohibited medication listed in [Table 5-2](#) presents undue safety risk for the patient, the patient should be discontinued from study drug as per [Section 5.6.2](#).

If the patient received a live virus vaccination during the study, the patient must discontinue study drug and complete the end-of-study visit.

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

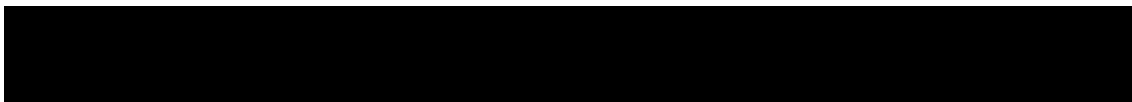


Table 5-2 Prohibited medication

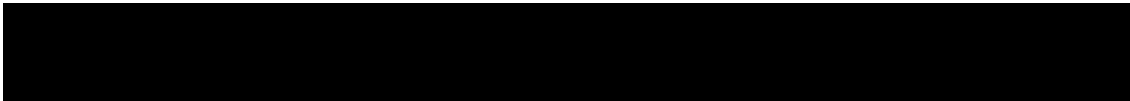
Prior Therapy (before Baseline Visit [Day 1])	
Prohibited medications^{†, ‡}	Washout period (before Baseline Visit [Day 1])
Any biologic drug directly targeting IL-17 or the IL-17RA (e.g. secukinumab, ixekizumab or brodalumab)	No prior use allowed
Alefacept, briakinumab, efalizumab, ustekinumab	6 months
Biological immunomodulating agents other than above (e.g. etanercept, adalimumab, infliximab)	12 weeks
Other systemic immunomodulating treatments [§] (e.g. methotrexate, cyclosporine A, corticosteroids (oral, i.v., intramuscular, s.c., intra-articular, transdermal) [§] , cyclophosphamide)	4 weeks
Other systemic psoriasis treatments (e.g. apremilast, retinoid, fumarates)	4 weeks
Photo chemotherapy (e.g. PUVA)	4 weeks
Phototherapy (e.g. UVA, UVB)	2 weeks
Live virus vaccinations	6 weeks
Any investigational treatment or participation in any interventional study	4 weeks or 5 half-lives (whichever is longer)
Prior Therapy (before Baseline Visit)	Stable period (before Baseline Visit [Day 1])
Any other treatment known to worsen psoriasis (e.g. beta-blockers, calcium channel blockers, lithium)	Stable at least 4 weeks before Baseline Visit (Day 1)

Abbreviations: PUVA: psoralen ultraviolet A; UVA: ultraviolet A; UVB: ultraviolet B

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

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

[§] Inhalative corticosteroids with only a topical effect (e.g. to treat asthma) and topical corticosteroids for ocular use (e.g. eye drops) are not considered “**systemic** immunomodulating treatments” and are therefore acceptable for use as comedication.



5.5.9 Exposure to light

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

5.5.10 Emergency breaking of assigned treatment code

Not applicable.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

Study completion is defined as all patients who have been enrolled at Baseline and completed the study as described in the protocol.

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

5.6.2 Discontinuation of study treatment

If discontinuation occurs for any reason in a treatment period (i.e. Treatment Period 1 or 2), the Investigator/qualified site staff must make every effort to determine the primary reason for the patient's discontinuation from the study. This information will then be recorded by Investigator/qualified site staff in the applicable eCRF section.

The study drug must be discontinued under the following circumstances:

- Withdrawal of informed consent.
- Emergence of the following AEs: AEs that in the judgment of the Investigator/qualified site staff (taking into account the patient's overall status) prevent the patient from continuing participation in the study (for example, sepsis or serious infection).
- Any laboratory abnormalities that in the judgment of the Investigator/qualified site staff (taking into consideration the patient's overall status) prevents the patient from continuing participation in the study.
- Pregnancy (see [Section 6.5.5](#) and [Section 7.3](#)).
- Use of prohibited treatment as per guidance in [Section 5.5.8](#).
- Any other protocol deviation that results in a significant risk to the patient's safety.

Patients discontinued from study drug will NOT be considered discontinued from the study. On the applicable section of the eCRF, the Investigator/qualified site staff must record the date and primary reason for stopping the study drug.

At the time of the study drug discontinuation visit,

- IF it has been at least 4 weeks after the last dose of study drug, THEN the assessments described for the end of Treatment Period 1 (EOT1) visit/Week 16 (for early discontinuation during Treatment Period 1) or the end of the Treatment Period 2 (EOT2) visit/Week 52 (for early discontinuation during Treatment Period 2) should be completed at this visit.

- IF it has not been at least 4 weeks after the last dose of study drug at the time of the study drug discontinuation visit, THEN the patient should be scheduled to return 4 weeks post last dose for their EOT1 visit (Week 16) or EOT2 visit (Week 52) assessments, respectively.

The Investigator/qualified site staff must contact the electronic study system on every study visit including when the patient completes the EOT1 visit (Week 16) or EOT2 Visit (Week 52) assessments to register the patient's completion of the study (Treatment Period 1 or 2, respectively) due to study drug discontinuation.

Patients who discontinue study drug should not be considered withdrawn from the study (except if the patient withdraws their informed consent).

See [Section 6](#) for the required assessments of these patients after study drug discontinuation. Patients who are discontinued from the study will not be replaced.

5.6.3 Withdrawal of informed consent

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

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

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

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the Investigator should show due diligence by contacting the patient, family or family physician as agreed in the informed consent process or later in the study and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until his/her scheduled end of study visit date has passed.

5.6.5 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as a discontinued patient as described in [Section 6](#). The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing the Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) of the early termination of the study or if prior agreed with Novartis, the sponsor or delegates could inform these institutions on behalf of the investigational site, if allowed as per local practice.

6 Visit schedule and assessments

Screening will be flexible in duration and is recommended not to exceed 4 weeks. The patients will sign the ICF, be evaluated for eligibility and will have all Screening visit assessments done as indicated in [Table 6-1](#).

[Table 6-1](#) lists all of the assessments and indicates with an “X” at which visits the assessments are performed. An ‘S’ indicates the data for that assessment are in the source documents at the study center.

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

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

The date of the new informed consent signature must be entered on the appropriate CRF page. Informed consent for a screened or rescreened patient must be obtained prior to performing any study-related assessment or collecting any data for the Screening Visit. For rescreening, all Screening assessments must be performed in accordance with the protocol, except for the TB work up, if applicable, if performed not more than 12 weeks prior to Day 1 (Baseline). If the date of the TB work-up is less than 12 weeks from Baseline then the TB work-up does not have to be repeated; however, the patient must repeat the QFT analyzed by the central laboratory.

During the study, patients may be seen at an unscheduled visit, e.g. if they experience deterioration of psoriasis or suspected AEs. During these unscheduled visits, study drug will NOT be administered.

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



Recommended visit windows

Treatment periods:

- ± 2 days for Visits 2, 3, 4, 5 and 9 (Baseline, Week 1, 2, 3, 4 and 16) in Treatment Period 1;
- ± 2 days for all study drug home administrations
- ± 5 days for all other study visits
- Visit 1 and Visit 2 must not be conducted on the same day and all relevant information for Visit 2 must be available before treating the patient. It is recommended that the Screening period does not exceed 4 weeks.


Patients who discontinue study drug prematurely for any reason (other than withdrawal of informed consent) before the end of the main treatment period will enter a 4 weeks post treatment follow-up period, unless the patient withdraws his/her informed consent, in which case an end-of study visit should be performed, if agreeable by the patient.

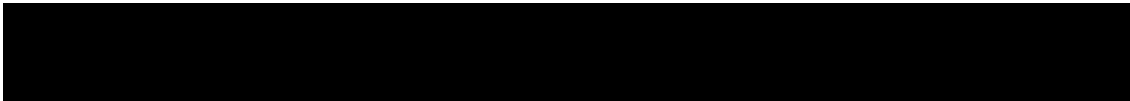
If a patient refuses to return for these assessments or is unable to do so, every effort should be made to contact them, or a knowledgeable informant, by telephone or by sending appropriate correspondence (i.e. certified letter) immediately. At this contact, the safety (e.g. potential occurrence of AEs or SAEs) and the primary reason for the patient's premature withdrawal should be determined. As a minimum, these patients will be contacted for safety evaluations during the 4 weeks following the last dose of study drug or the 30 days point following the last study visit (whichever is later). Documentation of attempts to contact the patient should be recorded in the patient source documents.

Possible order of assessments:

Overall, it has been estimated that completion of PROs may take up to a maximum of approximately 60 minutes; it is recommended that the PROs might be administered to patients in the same sequence at each visit.

Suggested guidelines for conduct of the visit assessments are provided below:

- Patient to complete PROs prior to any other study assessments or influence by the study site in the following order:
 - NRS (itching, scaling and pain VAS)
 - DLQI
 - EQ-5D[®]
 - HAQ[®]-DI (only for patients with concomitant PsA)
 - TSQM
 - PBI
- 
- Investigator/qualified site staff to complete Investigator/qualified site staff assessments.

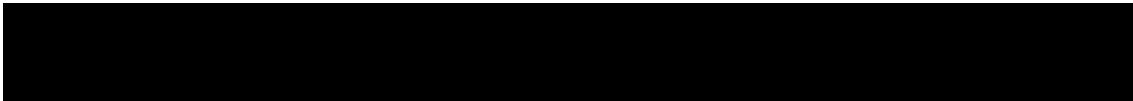


Recommended order is:

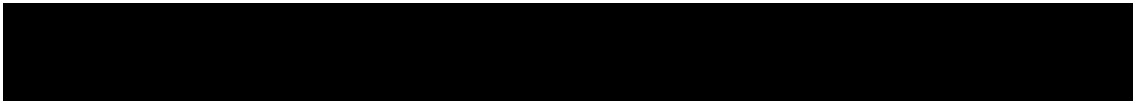
- IGA mod 2011
- PASI and BSA
- Physical examination
- All remaining study visit procedures (e.g. laboratory sample collection, vital signs measurements) must be completed prior to study drug dosing.
- Contact the electronic study system
- (Self-)Administration of study drug.

Table 6-1 Assessment schedule

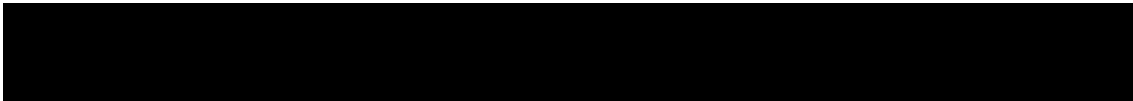
Period	Scr	Treatment Period 1								Treatment Period 2					Uns ^d	Comments
		2	3	4	5	6	7	8	EOT1	10	11	12	13	EOT2		
Visit	1	2	3	4	5	6	7	8	9 ^{a, b}	10	11	12	13	14 ^c		
Week	-4 to BL	BL	1	2	3	4	8	12	16	20	24	36	48	52		
Recommended visit window (days)		±2	±2	±2	±2	±5	±5	±5	±2	±5	±5	±5	±5	±5		
Informed consent	X															
Demographics	X															
Inclusion/exclusion criteria	X	X														These assessments are supported by and stored within the source documentation. Data relating to inclusion/exclusion criteria are captured in the corresponding eCRF.
Smoking history	X															
Cardiovascular history	X															
Psoriasis: medical history / previous psoriasis therapies	X															
Other medical history	X															
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
Height	X														X	
Weight	X	X							X					X	X	
Vital signs	X	X				X	X	X	X	X	X	X	X	X	X	



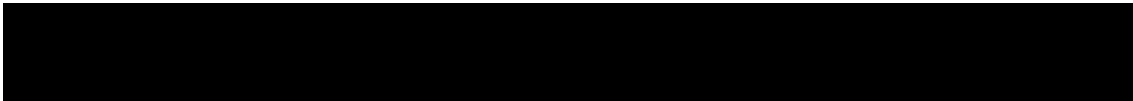
		Treatment Period 1							Treatment Period 2							
Period	Scr							EOT1					EOT2	Uns ^d	Comments	
Visit	1	2	3	4	5	6	7	8	9 ^{a, b}	10	11	12	13	14 ^c		
Week	-4 to BL	BL	1	2	3	4	8	12	16	20	24	36	48	52		
Recommended visit window (days)		±2	±2	±2	±2	±5	±5	±5	±2	±5	±5	±5	±5	±5		
Waist and hip circumference	X	X							X					X		
Laboratory sampling: safety panel (clinical chemistry, hematology, urine dipstick)	X	X				X		X	X	X	X	X	X	X	X	Samples will be shipped to the central laboratory for analysis. Urine dipstick to be used locally
Fasting labs: glucose, lipid panel, hsCRP, HbA1C		X							X				X	X		
QuantiFERON [®] TB-Gold in-tube test	X														X	
Serum pregnancy test	X														X	Only for females of child-bearing potential.
Urine pregnancy test (local)		X				X		X	X			X		X	X	In the event of a positive urine pregnancy test, study drug must be withheld and a serum pregnancy test performed at the same visit. A urine pregnancy test is not required for a woman who is sterile or who is post-menopausal.



		Treatment Period 1							Treatment Period 2						
Period	Scr							EOT1					EOT2	Uns ^d	Comments
Visit	1	2	3	4	5	6	7	8	9 ^{a, b}	10	11	12	13	14 ^c	
Week	-4 to BL	BL	1	2	3	4	8	12	16	20	24	36	48	52	
Recommended visit window (days)		±2	±2	±2	±2	±5	±5	±5	±2	±5	±5	±5	±5	±5	
Site assessments:															
IGA mod 2011	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PRO assessments:															
NRS (pain, itching and scaling VAS)		X				X		X	X		X	X	X	X	X
DLQI		X				X		X	X		X	X	X	X	X
EQ-5D [®]		X				X		X	X		X	X	X	X	X
HAQ [®] -DI		X				X		X	X		X	X	X	X	X
TSQM		X				X		X	X		X	X	X	X	X
PBI		X				X		X	X		X	X	X	X	X
AE assessment (including injection site reactions)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Registration, drug supply, or completion	X ^e	X	X	X	X	X	X	X	X	X	X	X	X	X ^f	^e Registration only ^f Completion only



		Treatment Period 1							Treatment Period 2						
Period	Scr							EOT1					EOT2	Uns ^d	Comments
Visit	1	2	3	4	5	6	7	8	9 ^{a, b}	10	11	12	13	14 ^c	
Week	-4 to BL	BL	1	2	3	4	8	12	16	20	24	36	48	52	
Recommended visit window (days)		±2	±2	±2	±2	±5	±5	±5	±2	±5	±5	±5	±5	±5	
Dispense study drug		X	X	X	X	X	X	X	X	X	X ^g	X ^g	X		^g including kits for home administration
Self-administration log											S	S	S	S ^h	S Patients must return the self-administration log along with all dispensed PFS and drug packaging at every visit. ^h in case of early discontinuation
Complete Screening period eCRF	X														
Complete end of main treatment period eCRF									X						
Complete end of treatment period eCRF													X		
Abbreviations: X = assessment to be recorded on clinical data base; S = assessment to be recorded on source documentation only AE: adverse event; BL: baseline; BSA: body surface area; eCRF: electronic case report form; DLQI: Dermatology Life Quality Index; EOT: end of treatment; EQ-5D [®] : EuroQOL 5 dimension; ██████████ HAQ [®] -DI: Health Assessment Questionnaire Disability Index; IGA Mod 2011: Investigator's Global Assessment Modified 2011; NRS: Numeric Rating Scale; PASI: Psoriasis Area and Severity Index; PBI: Patient Benefit Index; TSQM: Treatment Satisfaction Questionnaire for Medication															



The treatment administration schedule is presented in [Table 6-2](#).

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

Visit	9	10	11	12	13	14	15	16	17	18
Week	16	20	24	28	32	36	40	44	48	52
Recommended visit window (days)	±2	±5	±5	±2	±2	±5	±2	±2	±5	±5
Study drug administration	S	S	S	H	H	S	H	H	S	

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

6.1 Information to be collected on screening failures

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

For details on completing the eCRF please refer to the CRF completion guideline. In brief the Screening information such as the visit date, information on demography, informed consent, and the inclusion/exclusion criteria, must be completed. The AE eCRF should be completed for any AEs that occurred during the Screening period. Information on withdrawal of consent must be completed if consent is withdrawn during the Screening period. The Death eCRF should be completed in the case of death during the Screening period.

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

At the discretion of Investigators, abnormal test findings if judged clinically significant should be recorded after informed consent signature on the AE eCRF page.

6.2 Patient demographics/other baseline characteristics

All Baseline assessments should be performed prior to first study drug administration. These may occur during the Screening period or at the Baseline Visit depending on the assessment ([Table 6-1](#)).

6.2.1 Demographics

Patient demographic data to be collected on all patients include: date of birth, sex, race, ethnicity, height, weight and child-bearing potential (for females only).

6.2.2 Psoriasis medical history / previous psoriasis therapies

Patient's disease history will be collected at the Screening Visit. The information to be collected and entered as "psoriasis history" and "prior psoriasis therapies" includes the following:

- Date of first diagnosis of psoriasis prior to the Baseline Visit (by a physician).



- Previous treatments of psoriasis (including previous use of topical or systemic therapies as well as phototherapy and/or photochemotherapy) and the reason for discontinuation.
- Presence of PsA and the date of first diagnosis (by a physician).

6.2.3 Smoking history

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

6.2.4 Co-morbidities – cardiovascular medical history

Any information pertaining to cardiovascular medical history assessed prior to Screening should be reported as cardiovascular history in the eCRF. Cardiovascular risk factors should also be recorded.

6.2.5 Relevant medical history / current medical conditions

Relevant medical history and current medical conditions (not including psoriasis or PsA) present prior to signing the ICF will be recorded in the Medical History eCRF. Whenever possible, diagnoses and not symptoms will be recorded.

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

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

6.2.6 Prior and concomitant medications

Prior medications taken within the 6 months preceding the study Screening Visit (Visit 1), any other relevant medication taken before 6 months at the discretion of the Investigator and any concomitant medication irrespective of the start date will be captured in the eCRF.

6.2.7 Determination of tuberculosis status

Determination of TB status will be required before administration of study drug and should be performed as defined by local guidelines. TB status must be determined by medical history, signs, symptoms, and TB testing (via the QFT ([Section 6.2.7.1](#))).

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

6.2.7.1 QuantiFERON TB-Gold In-Tube assay

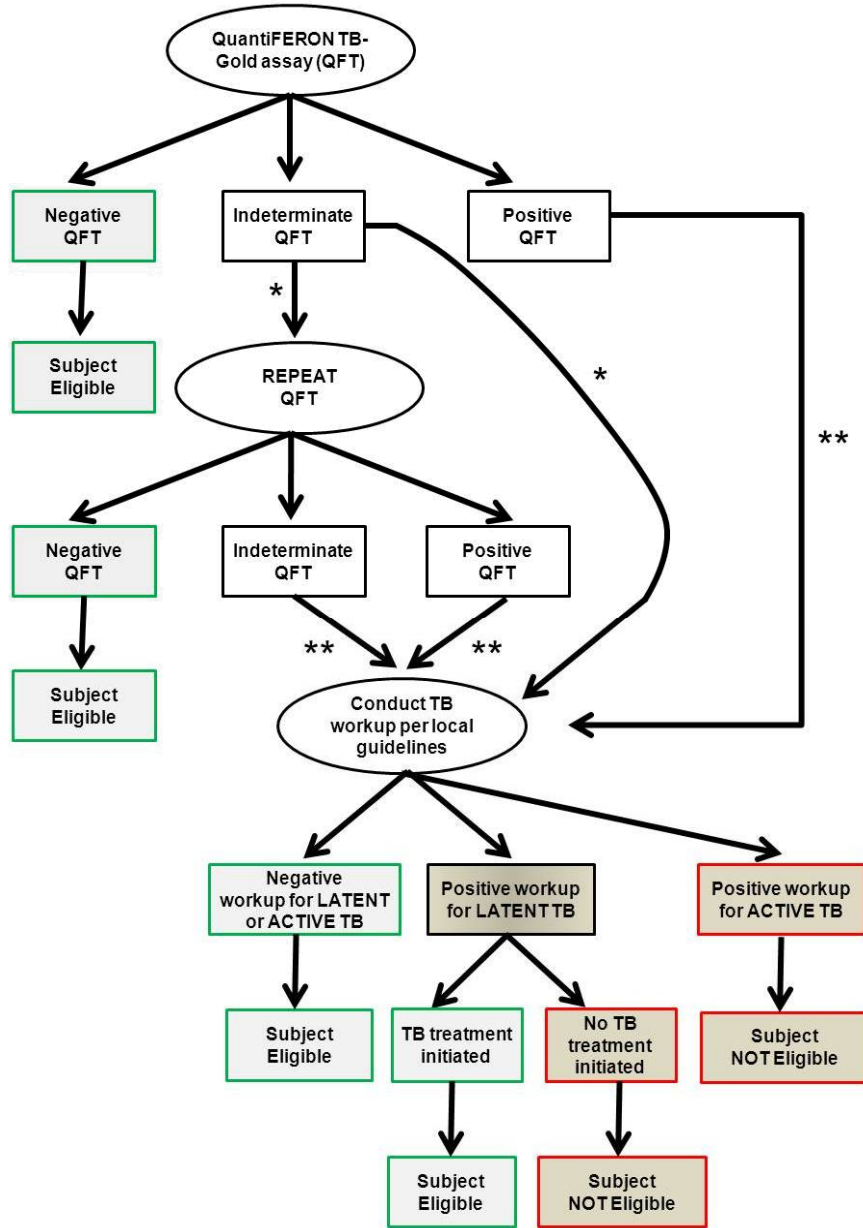
A QFT will be performed to assess the TB status at Screening for all patients. This test will only be used to determine patient's eligibility for the study. The test will be used to screen the patient population for latent TB infection ([Doherty et al 2008](#)).

This blood-based assay is specific for *Mycobacterium tuberculosis* and is not influenced by previous *Bacillus Calmette-Guérin* vaccination or exposure to other *Mycobacteria* species. This test, in contrast to the purified protein derivative skin test, is also insensitive to a booster effect since the patient is not exposed to the vaccine. The assay measures the production of interferon-gamma and presents it relative to a negative and a positive control sample ([Manuel](#)

and Kumar 2008). The QFT 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 Investigator/qualified study center staff in the laboratory manual (see Figure 6-1).

- If the test result is negative, the patient may be enrolled
- If the test result is positive, the Investigator should perform workup for the test result as per local procedures. If a TB workup was conducted prior to Screening the patient, results of the workup can be used to assess eligibility provided the workup was conducted within 12 weeks prior to Baseline.
 - Patients **positive** for latent TB per workup may be enrolled in the study if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration. Patients **positive** for active TB per workup are not eligible for the study.
 - Patients **negative** for TB (no signs of latent or active TB) per workup may be enrolled in the study.
- If the test result is **indeterminate**, it is **recommended to repeat the test once**. The Investigator may decide to skip the repetition of the test and proceed directly to the workup (but this is not recommended). If a TB workup was conducted prior to Screening the patient, results of the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to Day 1 (Baseline Visit).
 - If the second test is **negative**, the patient may be enrolled.
 - If the second test is **positive or indeterminate**, the Investigator should perform the work up as per local guidelines. The patient will not be eligible for enrollment if:
 - “active TB is present “or
 - if “latent TB is present” and is untreated as per local guidelines.Patients negative for TB per workup (no signs of latent or active TB) may be enrolled into the study if the workup was conducted within 12 weeks prior to Day 1 (Baseline Visit).
- If eligibility is being assessed with only 1 test result and a TB workup (i.e. no second TB test will be performed), the TB test to assess eligibility must have been done via the central laboratory for the study within the Screening period (within 4 weeks prior to Day 1 [Baseline Visit]) and the TB workup will only be considered if it was completed within 12 weeks prior to Baseline. Patients who are positive for latent TB per workup may be enrolled to the study if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration. Patients positive for active TB per workup are not eligible for the study. Patients negative for TB per workup (no signs of latent or active TB) may be enrolled in the study.

Figure 6-1 Tuberculosis screening flowchart



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

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

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

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

6.2.8 Other Baseline characteristics

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

- Vital signs, hematology, clinical chemistry, urine, fasting lab tests (glucose, lipid panel, HbA1c and hsCRP), physical examination, height, weight, past medical history record of HIV, hepatitis B virus, and hepatitis C virus history. A urine pregnancy test will be performed for women of child-bearing potential.
- Baseline efficacy assessments of IGA mod 2011, PASI and BSA.
- Baseline PRO assessments of DLQI, EQ-5D[®], NRS (itching, scaling and pain VAS), HAQ[®]-DI (only for patients with concomitant PsA), TSQM and PBI.
- [REDACTED]

6.3 Treatment exposure and compliance

All doses of study drug administration will be recorded in the eCRF. Patient compliance to the study drug should be assessed by qualified study center personnel at each study visit using the study kits and documentation regarding study drug dispensation and administration.

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

6.4 Efficacy

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

6.4.1 Investigator's global assessment (IGA mod 2011)

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

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

The IGA mod 2011 rating scale for overall psoriatic disease is shown in [Table 6-3](#).

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

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

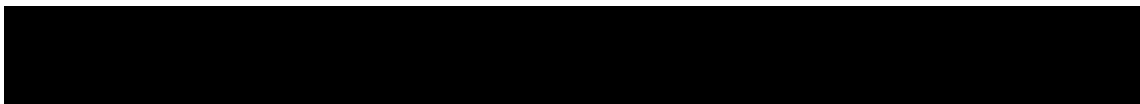


Table 6-3 The IGA mod 2011 rating scale

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

Note: Involvement of nails is not part of the assessment

6.4.2 Assessment of psoriasis area and severity index (PASI) and total body surface area (BSA)

The Investigator or trained qualified designee will complete the PASI assessment as indicated in [Table 6-1](#). Whenever possible, the same evaluator should perform this assessment at all visits. The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for full details of the PASI assessment). The following calculations will be done: each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added to estimate the total BSA affected by plaque-type psoriasis.

The PASI score ([Fredriksson and Pettersson 1978](#); [Weisman et al 2003](#); [Gottlieb et al 2006](#)) will be derived as indicated in [Table 6-4](#). The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the 4 body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details to help with the assessment are provided below:

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

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

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

The keys for the letters are provided in [Table 6-4](#).

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0. The Baseline value for analysis of PASI is collected at Day 1

(Baseline Visit). Patients require a total BSA affected by plaque-type psoriasis of $\geq 10\%$ and a PASI score of $\geq 10\%$ at Baseline to be eligible for this study.

Table 6-4 The PASI scoring system

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

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

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

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

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

6.4.3 Definitions of efficacy variables based on PASI

The following definitions will be used in this study based on the EMA guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr):

- **PASI 50 response (partial response):** patients achieving $\geq 50\%$ improvement (reduction) in PASI score compared to Baseline are defined as PASI 50 responders.
- **PASI 75 response:** patients achieving $\geq 75\%$ improvement (reduction) in PASI score compared to Baseline are defined as PASI 75 responders.

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

6.4.4 Appropriateness of efficacy assessments

All evaluation tools used in this study have been used previously in clinical trials for psoriasis. Evaluation of disease severity based on clinical scoring is commonly used in dermatology.

6.5 Safety

From Day 1 (Baseline Visit), all blood draws and safety assessments must be performed as indicated in [Table 6-1](#) prior to study drug administration. Appropriate safety assessments (e.g. evaluation of AEs and SAEs) should be repeated after the dose of study drug is administered.

- Evaluation of all AEs and SAEs including injection site hypersensitivity reactions, vital signs, laboratory assessments and occurrence of infections (see [Section 7](#)).
- Physical examination.
- Vital signs.
- Height and weight.
- Laboratory evaluations (hematology, clinical chemistry, urine dipstick).
- Fasting laboratory tests (glucose, lipid profile, HbA1c and hsCRP).
- Pregnancy and assessments of fertility.

6.5.1 Physical examination

A physical examination, including general appearance, will be performed as indicated in [Table 6-1](#).

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

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

Information for all physical examinations must be included in the source documentation at the study center. Significant findings that are present prior to the patient signing informed consent must be included in the eCRF. Significant findings made after the signing of the informed consent which meet the definition of an AE must be recorded on the eCRF ([Section 7](#)).

6.5.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed as indicated in [Table 6-1](#). After the patient has been sitting for 5 minutes, with back supported and both feet placed on the floor, **systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be measured twice** (1 to 2 minutes apart) using a validated device with an appropriately sized cuff ([Mancia et al 2007](#)); each BP measurement will be recorded in the source. In case the cuff sizes available are not large enough for the patient's arm, a sphygmomanometer with an appropriately sized cuff may be used.

If possible, assessments should be performed per patient by the same study center staff member throughout the study.

Normal blood pressure will be defined as a SBP of 90 to < 120 mmHg, and a DBP of 60 to < 80 mmHg under the measurement conditions outlined above. Notable blood pressure will be hypertension (SBP of \geq 140 mmHg and/or DBP of \geq 90 mmHg) or hypotension (SBP of < 90 mmHg and/or a DBP of < 60 mmHg). A blood pressure indicative of pre-hypertension (SBP of 120 to < 140 mmHg and/or DBP of 80 to < 90 mmHg) will not be regarded as notable ([Chobanian et al 2003](#)).

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

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

6.5.3 Height, weight, waist and hip circumference

Height and body weight will be measured at the times indicated in [Table 6-1](#). Height and body weight will be measured in indoor clothing, but without shoes.

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

Waist and hip circumference will be measured at the times indicated in [Table 6-1](#). According to the World Health Organization (WHO) data gathering protocol ([STEPwise approach to surveillance, 2008](#)), the waist circumference should be measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, using a stretch resistant tape that provides a constant 100 g tension. Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor.

For both measurements, the individual should stand with feet close together, arms at the side and body weight evenly distributed, and should wear little clothing. The patient should be relaxed, and the measurements should be taken at the end of a normal expiration. Each measurement should be repeated twice; if the measurements are within 1 cm of one another, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

6.5.4 Laboratory evaluations

Patients should avoid smoking within the hour preceding blood draws.

A central laboratory will be used for analysis of all specimens unless otherwise noted (e.g. urine dipsticks will be locally used). Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the laboratory manual. The laboratory manual should also be consulted for the identification of notable values.



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

6.5.4.1 Hematology

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

6.5.4.2 Clinical chemistry

Serum chemistry will include urea, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase, and alkaline phosphatase (ALP). Serum chemistry will be measured at all scheduled study visits within the visit window specified in [Table 6-1](#).

6.5.5 Pregnancy and assessments of fertility

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

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

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

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

6.5.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

6.6 Other assessments

Health-related QoL(HR-QoL) assessments should be obtained as shown in [Table 6-1](#). Assessments can be collected either by using paper forms or with support of an electronic system.

6.6.1 Health-related quality of life

The impact of psoriasis on various aspects of a patient's HR-QoL will be assessed by the following validated instruments, each of which will be performed as indicated in [Table 6-1](#):

- NRS (itching, scaling and pain VAS)
- DLQI
- [REDACTED]
- EQ-5D[®]



- HAQ[®]-DI
- TSQM
- PBI

All these QoL assessments should be completed by the patient [REDACTED] before they see the study physician (Investigator or designee) who will perform the Investigator assessments. All assessments will be completed in the language the respondent is most familiar with, at the scheduled visit before the patient sees the Investigator for clinical assessments. The respondent should be given sufficient space and time to complete the questionnaires. The study coordinator should check the questionnaires for completeness and encourage the respondent to complete any missing responses. Prior to clinical examination, the Investigator should review the completed questionnaires for responses that may indicate potential AEs or SAEs.

If AEs or SAEs are confirmed, the Investigator must record the events as per the instructions in [Section 7](#).

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

6.6.1.1 Numeric rating scale: patient's assessment of pain, itching and scaling

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

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

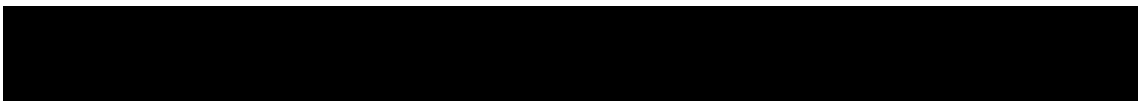
Patients have to rate their pain, itching, and scaling from 0 to 10 (11-point scale), with the understanding that 0 represents the absence or null end of the pain, itching, or scale intensity (i.e. no pain, itching or scaling) and 10 represents the other extreme of pain, itching, or scaling intensity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

The NRS scale will be completed by the patient as indicated in [Table 6-1](#).

6.6.1.2 Dermatology life quality index

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

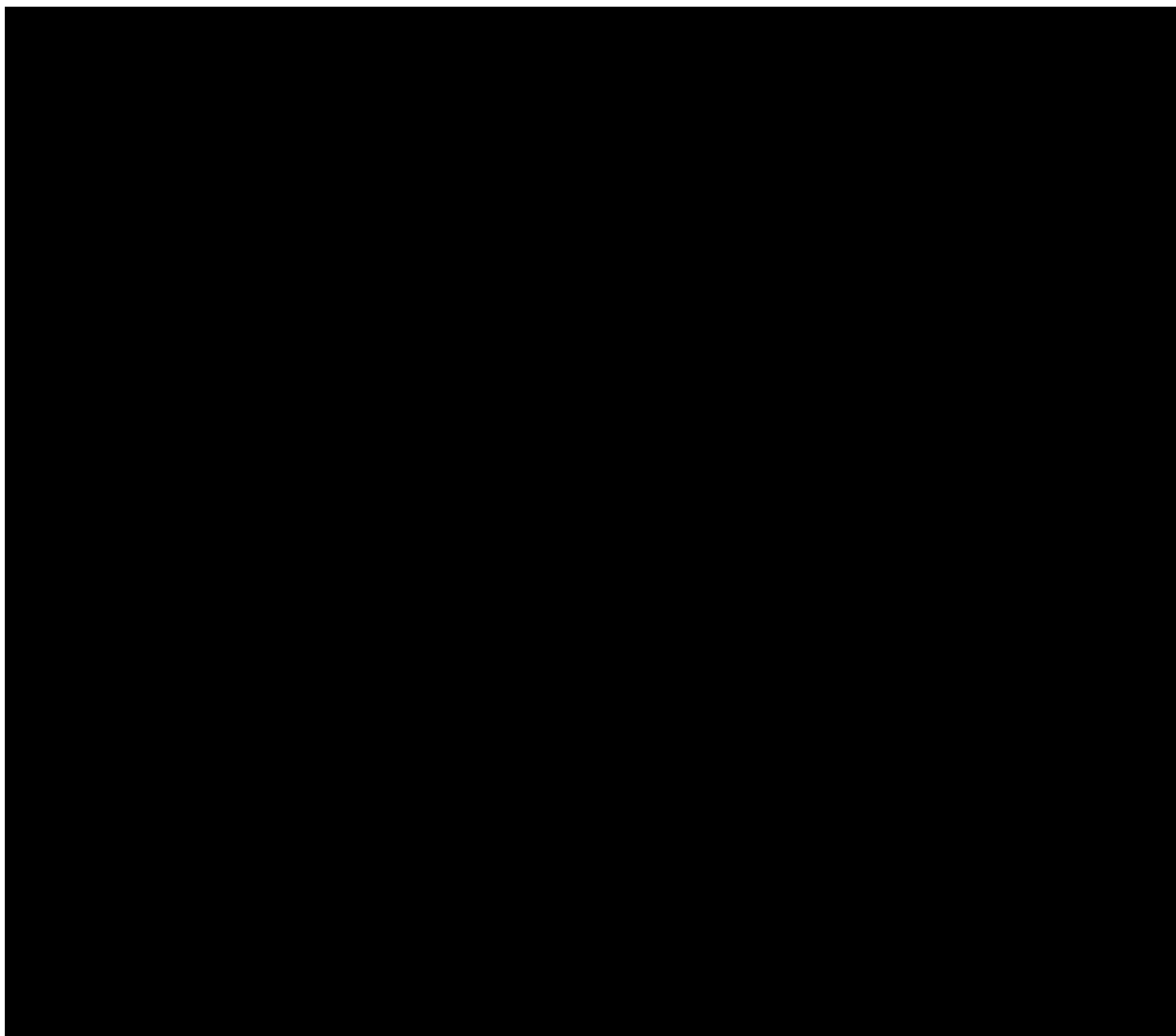
The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 33 different skin conditions and is available in 85 languages. The DLQI is the most frequently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



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

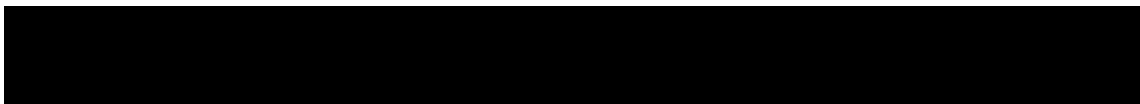
Each item has 4 response categories ranging from 0 (not at all) to 3 (very much). “Not relevant” is also a valid response and is scored as 0. The DLQI[®] total score is a sum of the 10 questions. Scores range from 0 to 30, with higher scores indicating greater health-related QoL impairment. Each subscale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

The DLQI questionnaire will be completed by the patient as indicated in [Table 6-1](#).



6.6.1.4 EuroQOL 5-Dimension Health Questionnaire

The EQ-5D[®] is a generic instrument developed by the EuroQoL group to assess patients' health status for clinical and economic appraisal, which was introduced in 1990 ([The EuroQol Group 1990](#)). Available in over 100 official language versions, it provides a simple descriptive profile and a single index value for health status. The recall period is “today”, and the instrument takes 1 to 2 minutes to complete. The instrument essentially consists of 2 pages; the EQ-5D[®] descriptive system and the EQ-5D[®] VAS. The EQ-5D[®] descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort



and anxiety/depression. Each dimension has 5 response levels: no problems, slight problems, moderate problems, severe problems and unable. The patient is asked to indicate the patient's health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions.

A unique health state is defined by combining 1 level from each of the 5 dimensions. Health states may be converted into a single number, called weighted index, by applying values (also called weights) to each of the levels in each dimension (Dolan 1997). The weighted index constitutes a measure of utility. The VAS records the respondent's self-rated health on a vertical 20-cm VAS where the endpoints are labelled "best imaginable health state" and "worst imaginable health state." This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

The EQ-5D[©] questionnaire will be completed by the patient as indicated in Table 6-1.

6.6.1.5 Health assessment questionnaire – disability index (subjects with PsA only)

The Health Assessment Questionnaire (HAQ[©]) was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a patient's level of functional ability and activity restriction. Although originally developed for use in subjects with rheumatic disease, the HAQ[©] has been employed across a large variety of disease areas. The disability assessment component of the HAQ[©], the HAQ[©]-DI (Health Assessment Questionnaire – Disability Index) assesses a patient's level of functional ability and includes questions on fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 items in 8 categories of functioning including dressing and grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to..." perform a particular task. Each item is scored on a 4-point scale from 0 to 3, representing normal, no difficulty (0), some difficulty (1), much difficulty (2), and unable to do (3). The HAQ[©]-DI also includes questions about the use of 'aids or devices' and aid from other people to supplement the answers given to the 20 items.

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

The questionnaire will be completed by the subject as specified in Table 6-1 by all patients with a medical history of PsA recorded in the eCRF during the Screening period.

6.6.1.6 Treatment satisfaction questionnaire for medication

The 14-item TSQM (TSQM Version 1.4) is a reliable and valid instrument to assess patient satisfaction with medication, providing scores on 4 scales; side effects (3 items), effectiveness (5 items), convenience (3 items) and global satisfaction (3 items). In naturalistic studies, administering the TSQM with the side effects domain could provoke the physician to assess the presence or absence of AEs in a way that is clinically atypical, carrying the potential to interfere with routine medical care. As a result, an abbreviated 9-item TSQM (TSQM-9), derived from the TSQM Version 1.4 but without the 5 items of the side effects domain was created. The TSQM-9 provides a suitable measure of treatment satisfaction with medication in

studies where measuring patient-reported side effects has a potential to interfere with the study objectives. This abbreviated TSQM will be used in this study (Bharmal et al 2009) as specified in Table 6-1.

6.6.1.7 Patient benefit index

The PBI is based on questioning the patient about the importance of individual therapy needs from a standardized list prior to treatment and presenting these items again during or after completion of the treatment, with the patient being asked to rate the extent to which the previous objectives were achieved through treatment (Augustin et al 2009). The achieved benefits according to the individual needs can finally be weighted. The PBI was developed and validated for skin diseases in general (Augustin et al 2009), but a range of disease specific PBI versions has been developed, including psoriasis (Feuerhahn et al 2012).

The questionnaire includes 23 items on patient-relevant therapy needs and benefits. The first part of the instrument, the 'Patient Needs Questionnaire' (PNQ), is filled in by the patients before therapy. A 5-step Likert scale (0 = 'not important at all' to 4 = 'very important') records the individual relevance of the different items to the patients. The second part, the PBQ, is filled in by the patients during or after therapy. It comprises the same items as the PNQ, but in contrast, the patients evaluate the extent to which the treatment needs have been fulfilled by therapy (scaled from 0 = 'treatment did not help at all' to 4 = 'treatment helped a lot'). In addition, the Likert scale contains the option 'does not apply to me' in the PNQ and the option 'did not apply to me' in the PBQ. The needs prior to treatment (PNQ) and the benefits achieved by treatment (PBQ) are converted to a weighted index value, the PBI in the narrower sense. It can have a value from 0 = 'no benefit' to 4 = 'maximal benefit'. A PBI value of C1 is considered as relevant benefit.

The PBI questionnaire will be completed by the patient as indicated in Table 6-1.

6.6.2 Resource utilization

Not applicable.

6.6.3 Pharmacokinetics

Not applicable.

6.6.4 Other biomarkers

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

7 Safety monitoring

7.1 Adverse events

An AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a patient or clinical investigation patient *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Study drug includes the study drug under evaluation and the comparator treatment that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered AEs if they worsen after starting the study drug. All patients who have signed informed consent and are entered into the next period of the study will have all AEs **occurring after informed consent is signed** recorded on the AE CRF.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. Adverse events may also be detected when they are volunteered by the patient during or between visits or through physical examinations, laboratory tests, or other assessments.

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

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

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

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

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

A SAE is defined as event which:

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

Is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events. All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see [Section 7.2](#).

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

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

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

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

7.2 Serious adverse event reporting

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

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

Information about all SAEs (either initial or follow-up information) is collected and recorded in English on the paper SAE Report Form or the electronic SAE Form within the data capture system (where available). The Investigator must assess the relationship to each specific component of the study drug (if the study drug consists of several components).

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

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

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study drug a DS&E Department associate may urgently require further information from the Investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification to inform all Investigators involved in any study with the same study drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the Competent Authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Pregnancy reporting

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the Investigator/qualified study center staff to the local Novartis DS&E Department. Pregnancy

follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug.

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a study center initiation visit or at an Investigator's meeting, a Novartis representative will review the protocol and eCRFs with the Investigators and their staff. During the study, the field monitor will visit the study center regularly to check the completeness of patient records, the accuracy of entries in the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for as appropriate. Key study personnel must be available to support the field monitor during these visits.

In addition, monitoring of treatment accountability will be performed continuously by a field monitor during study center visits and at the completion of the study. The field monitor will regularly check that study drug is being stored, prepared, dispensed and accounted as appropriate.

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

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

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

8.2 Data collection

Designated Investigator staff (at the study centers) will enter the data required by the protocol into the eCRF system. Designated Investigator 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 study center staff. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the Investigator will receive copies of the patient data for archiving at the study center.

8.3 Database management and quality control

Novartis staff (or designated contract research organization (CRO) staff) review the data entered into the CRFs by Investigator/qualified study center staff for completeness and accuracy and instruct the study center personnel to make any required corrections or additions.

Queries are sent to the study center using an electronic data query. The Investigator/qualified study center staff are required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the study center. Study center personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database. The signed copy of the Data Query Form is kept at the Investigator study center.

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

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

Medical history and AEs will be coded using MedDRA terminology.

Efficacy assessments (IGA mod 2011, PASI and BSA) will be performed using an electronic device or paper forms. In case electronic devices are used but there is a data collection failure, a paper-based process is acceptable and details of the whole process are described in a separate user manual.

PROs assessments (DLQI, EQ-5D[®], NRS (itching, scaling and pain VAS), HAQ[®]-DI, TSQM and PBI) will be performed using electronic devices or paper forms. In case electronic devices are used but there is a data collection failure a paper-based process is acceptable and details of the whole process are described in a separate user manual.

All efficacy assessments and PRO assessments will be maintained in a central database and in case the database is managed by a vendor results will be sent electronically to Novartis (or a designated CRO).

Data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an electronic study system. The system will be either supplied by a vendor or Novartis directly, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO) in case a vendor is used.

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 made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis study management.

8.4 Data monitoring committee

In alignment with the EMA Guideline on Data Monitoring Committees (EMA/CHMP/EWP/5872/03 Corr) no Data Monitoring Committee (DMC) is deemed to be required for this Phase 4 clinical study. A pharmacovigilance review concluded that substantial amount of safety data for the study drugs have been collected through all study phases and that a DMC would not be beneficial for the study.

8.5 Adjudication committee

Not applicable.

9 Data analysis

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

If not otherwise specified, p-values will be presented as two-sided p-values and 2-sided CIs will be displayed.

9.1 Analysis sets

The following analysis sets will be used in the analyses:

Enrolled set: All patients who are enrolled are included in the Enrolled set.

Safety set: The Safety set includes all patients who received at least one dose of study drug.

Full Analysis set: The Full Analysis set includes all patients who received at least one dose of study drug.

9.2 Patient demographics and other baseline characteristics

Demographics and other Baseline characteristics will be collected at Screening (Visit 1) or at Baseline (Visit 2) prior to first study drug administration for the efficacy and PRO measurements. Summary statistics will be provided for demographic and Baseline characteristics. Data will be summarized for the overall population as well as for the 3 pre-defined subpopulations with absolute counts and relative frequencies for categorical variables and with mean, standard deviation, minimum, median, and maximum for continuous variables.

Patient background information (medical history and current medical conditions) will be summarized by MedDRA primary SOC and preferred term. Summaries for psoriasis specific medical history and cardiovascular medical history will also be provided.

9.3 Treatments

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

Duration (days) of exposure to study drug will be summarized. The number of secukinumab injections will be presented by visit and cumulatively.

Patients who prematurely discontinue the study drug will be listed along with the reason for discontinuation.

Compliance will be calculated in percent as the number of injections administered divided by the number of injections scheduled according to the protocol.

9.3.1 Prior and concomitant medications

Prior and concomitant medications will be summarized by prior psoriasis treatment subpopulation in separate tables.

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

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

9.4 Analysis of the primary variable

9.4.1 Variable

The primary analysis variable is the proportion of patients achieving a DLQI 0/1 response at Week 16 in 3 pre-defined subpopulations and in the overall study population.

The analysis of the primary variable will be based on the Full Analysis set.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis of this study will be descriptive without any formal group comparisons or hypothesis testing. The absolute and relative frequencies of patients achieving a DLQI 0/1 response at Week 16 will be calculated for the subpopulations defined above as well as for the overall study population. For the proportions, (descriptive) 95% CIs will additionally be reported.

9.4.3 Handling of missing values/censoring/discontinuations

The last observation carried forward (LOCF) method will be applied to the continuous variables of DLQI score, PASI score and IGA mod 2011 score that are missing after Baseline regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues). The binary response variables based on DLQI score, PASI score and IGA mod 2011 score will be derived from these imputed values, this means that a patient with missing values will be counted as a non-responder unless he already achieved the respective response criterion at the last available measurement.

Any missing individual items are treated as missing data. Cases for which a weekly score cannot be calculated (less than four completed days) will not be included in the analysis. The percent of missing and missing patterns for each item will be assessed.

9.4.4 Sensitivity analyses

No sensitivity analysis will be performed.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

All secondary objectives (as defined under [Section 2.2](#)) will be analyzed descriptively, similarly to the primary endpoint. Relative and absolute frequencies will be presented for categorical variables and mean, SD, median, minimum and maximum will be presented for continuous variables.



9.5.2 Safety variables

Analysis of safety data will be based on the Safety set.

Adverse events

The assessment of safety will be based primarily on the frequency of AEs and SAEs. SAEs suspected by the Investigators to be related to the prescribed medication will be summarized as appropriate.

The only AEs that will be counted will be treatment-emergent AEs (TEAEs). A TEAE is defined as any AE that develops after initiation of the study treatment or any event already present that worsens following exposure to the study treatment. This definition is not used by the Investigator, but rather is used in the analysis and reporting of clinical trial data. A patient with multiple AEs within a body system will only be counted once towards the total of this body system.

The incidence of AEs (new or worsened) will be summarized by primary SOC, preferred term, severity and relationship to study drug. In addition, the incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary SOC and preferred term.

All AEs will be displayed by group and patient.

Vital signs

All vital signs (including height and weight) will be summarized by prior psoriasis treatment group and visit and listed by group, patient and time. Analysis of the vital sign measurements using summary statistics for the change from Baseline for each post-Baseline visit will be performed.



Clinical laboratory evaluations

The summary of laboratory evaluations will be presented for the hematology, clinical chemistry, and fasting laboratory tests. Descriptive summary statistics for the change from Baseline to each visit will be presented. These descriptive summaries will be presented by laboratory test and prior psoriasis treatment group. Changes from Baseline will only be summarized for patients with both Baseline and post Baseline data.

Shift tables will be provided for all parameters to compare a patient's Baseline laboratory evaluation relative to the most extreme observed value during the treatment phase. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the Baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment group. Shifts will be presented by visit as well as for most extreme values post-Baseline.

Physical examinations

All physical examination data will be listed by prior psoriasis treatment group, patient and visit and summary statistics will be provided by prior psoriasis treatment group and visit.

Pregnancy tests

Serum and urine pregnancy tests where applicable will be summarized and listed.

9.5.3 Health-related quality of life

The analysis of the HR-QoL assessments in [Section 6.6.1](#) is described in the SAP.

9.5.4 Resource utilization

Not applicable.

9.5.5 Pharmacokinetics

Not applicable.

9.5.6 Pharmacogenetics/pharmacogenomics

Not applicable.

9.5.7 Biomarkers

If a biomarker sub study is performed, details will be described in a separate study protocol.

9.5.8 PK/PD

Not applicable.



9.6 Interim analyses

An interim analysis describing the self-reported Baseline characteristics and HR-QoL of patients prior to treatment may be performed for this study after LPFT. Details will be described in the Statistical Analysis Plan (SAP).

9.7 Sample size calculation

The study aims to estimate primarily the effect of 16 weeks treatment with secukinumab 300 mg on the QoL of the overall study population as well as within the 3 pre-defined subpopulations. It is expected that 40% of the overall study population will fulfil the criteria for the definition of subpopulation A; 40% will fulfil the criteria for subpopulation B; and 20% will fulfil the criteria for subpopulation C.

The DLQI 0/1 response rate in the overall population treated with secukinumab 300 mg s.c. is expected to be around 70% at Week 16; however, it may vary within those pre-defined subpopulations. A total of 323 patients are required to estimate the response rate of DLQI 0/1 with a precision (= 95% CI) of 5% if the true response rate is about 70% in the smallest subpopulation. To ensure that this precision is achieved in the 3 subpopulations (defined in [Section 3.1](#)), which consist of 20% to 40% of the overall study population, 1 615 patients in total should be recruited into this trial.

10 Ethical considerations

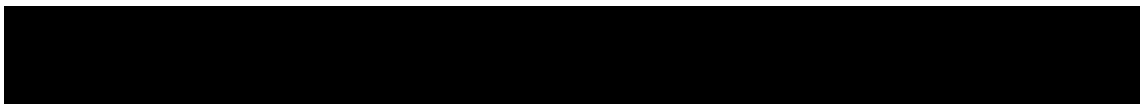
10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH GCP, with applicable local regulations (including European Directive 2001/20/EC, and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

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

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



Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.



10.3 Responsibilities of the investigator/qualified site staff and IRB/IEC

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

10.4 Publication of study protocol and results

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

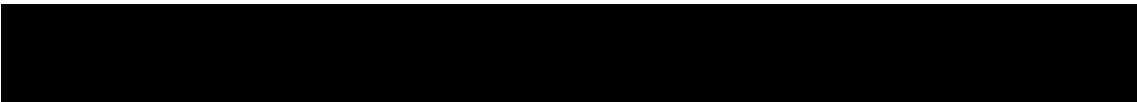
11 Protocol adherence

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

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

11.1 Protocol amendments

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



implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in [Section 7](#) Safety Monitoring must be followed.

12 References

Albrecht L, Bourcier M, Ashkenas J et al (2011) Topical psoriasis therapy in the age of biologics: evidence-based treatment recommendations . *J Cutan Med Surg*; 15(6):309-21.

Augustin M, Schaefer I, Rabini S, et al (2009) Assessing the value of supportive skin care: development and validation of an instrument for evaluating patient-relevant benefit. *Dermatology*; 218:255–59.

Augustin M, Radtke MA, Zschocke I, et al (2009b) Patient benefit index: a novel approach in patient-defined outcomes measurement for skin disease. *Arch Dermatol Res*; 301:561–71.

Augustin M, Reich K, Glaeske G et al (2010) Co-morbidity and age-related prevalence of psoriasis: analysis of health insurance data in Germany. *Acta Derm Venereol*; 90(2):147-51.

Augustin M, Holland B, Dartsch D et al (2011) Adherence in the treatment of psoriasis: a systematic review. *Dermatology*; 222(4):363-74.

Basra MK, Sue-Ho R, Finlay AK et al (2007) The Family Dermatology Life Quality Index: measuring the secondary impact of skin disease. *Br J Dermatol*; 156(3):528-38.

Basra MK, Fenech R, Gatt RM et al (2008) The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol*; 159(5):997-1035.

Bharmal M, Payne K, Atkinson M, et al (2009) Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. *Health Qual Life Outcomes*; 7:36.

Bhutani T, Patel T, Koo B et al (2013) A prospective, interventional assessment of psoriasis quality of life using a non skin-specific validated instrument that allows comparison with other major medical conditions. *J Am Acad Dermatol*; 69(2):e79-e88.

Blauvelt A, Prinz JC, Gottlieb AB et al (2015). Secukinumab administration by pre-filled syringe: efficacy, safety, and usability results from a randomized controlled trial in psoriasis (FEATURE). *Br J Dermatol*; 172(2):484-93.

Callis Duffin K, Yeung H, Takeshita J, et al (2014) Patient satisfaction with treatments for moderate-to-severe plaque psoriasis in clinical practice. *Br J Dermatol*; 170(3):672-80.

Chobanian AV, Bakris GL, Black HR (2003) Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*; 42: 1206-52.

Christophers E (2007) Comorbidities in psoriasis. *Clin Dermatol*; 25 (6):529-34.

Committee for medicinal products for human use (CHMP), European Medicines Agency for

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

Committee for human medicinal products for human use (CHMP), European Medicines Agency for the Evaluation of Medicines for Human Use (2005) Guideline on data monitoring committees. EMEA/CHMP/EWP/5872/03 corr. London, UK.

Doherty SD, Van Voohees A, Lebwohl MG (2008) National psoriasis foundation consensus statement on screening for latent tuberculosis infection in patient with psoriasis treated with systemic and biologic agents. *J Am Acad Dermatol*; 59 (2):209-17.

Dolan P (1997). Modeling valuations for EuroQol health states. *Med Care* 35(11):1095-108.

Driessen RJ, Bisschops LA, Adang EM, et al (2010). The economic impact of high-need psoriasis in daily clinical practice before and after the introduction of biologics. *Br J Dermatol*; 162(6):1324-9.

Eskin M, Savk E, Uslu M, et al (2014) Social problem-solving, perceived stress, negative life events, depression and life satisfaction in psoriasis. *J Eur Acad Dermatol Venereol*; 28(11): 1553-9.

Feldman SR, Krueger GG (2005) Psoriasis assessment tools in clinical trials *Ann Rheum Dis*2005;64:ii65-ii68.

Feuerhahn J, Blome C, Radtke M et al (2012) Validation of the patient benefit index for the assessment of patient-relevant benefit in the treatment of psoriasis. *Arch Dermatol Res*; 304:433–41.

Finlay AY and Coles EC (1995) The effect of severe psoriasis on the quality of life of 369 patients. *Br J Dermatol*; 132(2): 236–244.

Finlay AY and Khan GK (1994). Dermatology Life Quality Index (DLQI): A simple practical measure for routine clinical use. *Clin Exp Dermatol*; 19:210-216.

Fredriksson T and Pettersson U (1978) Severe psoriasis-oral therapy with a new retinoid. *Dermatologica*; 157:238-44.

Fries JF, Spitz PW and Young DY (1982) The dimensions of health outcomes: the Health Assessment Questionnaire, Disability and Pain scales. *J Rheumatol*; 9(5): 789-93.

Gladman DD (2004) Psoriatic arthritis. *Dermatol Ther*; 17:350-63.

Gladman DD, Antoni C, Mease P et al (2005) Psoriatic arthritis: epidemiology, clinical features, course and outcome; *Ann Rheum Dis*; 64 (Suppl 2):ii14-7.

Gniadecki R, Robertson D, Molta CT, et al (2012) Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. *J Eur Acad Dermatol Venereol*; 26(11):1436-43.

Gottlieb AB, Hamilton T, Ivor C, et al (2006) Long-term continuous efalizumab therapy in patients with moderate to severe chronic plaque psoriasis: updated results from an ongoing trial for the Efalizumab Study Group. *J Am Acad Dermatol*; 54(4):S154-S163.

Griffiths CE, Sterry W, Brock F, et al (2015) Pattern of response in patients with moderate-to-severe psoriasis treated with etanercept. *Br J Dermatol*;172(1):230-8.

- Henseler T and Christophers E (1995) Disease concomitance in psoriasis. *J Am Acad Dermatol*; 32(6):982-6.
- Heydendael VM, de Borgie CA, Spuls PI et al (2004) The burden of psoriasis is not determined by disease severity only. *J Invest Dermatol Symp Proc*; 9(2):131-5.
- Ibrahim G, Waxman R and Helliwell PS (2009) The prevalence of psoriatic arthritis in people with psoriasis. *Arthritis Rheum*; 61(10):1373-8.
- Kagami S, Rizzo H, Lee JJ, et al (2010) Circulating Th17, Th22, and Th1 Cells are increased in psoriasis. *J Invest Dermatol*; 130:1373-83.
- Katugampola RP, Lewis VJ, Finlay AY (2007). The Dermatology Life Quality Index assessing the efficacy of biological therapies for psoriasis. *Br J Dermatol*; 156(5):945-50.
- Langley RGB, Feldman SR, Nyirady J, et al (2013) The 5-point Investigator's Global Assessment (IGA) Scale: a modified tool for evaluating plaque psoriasis severity in clinical trials *J Dermatolog Treat*. 2015 Feb;26(1):23-31.
- Langley RG, Elewski BE, Lebwohl M, et al (2014) Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med*; 371(4):326-38.
- Lebwohl M, Papp K, Han C, et al (2010) Ustekinumab improves health-related quality of life in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial. *Br J Dermatol*; 162(1):137-46.
- Lebwohl M, Bachelez H, Barker J, et al (2014) Patient perspectives in the management of psoriasis: results from the population based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol*; 70(5): 871-81.
- Linder D, Dall'Olio E, Gisondi P, et al (2009) Perception of disease and doctor-patient relationship experienced by patients with psoriasis: a questionnaire-based study. *Am J Clin Dermatol*; 10(5):325-30.
- Lowes MA, Kikuchi T, Fuentes-Duculan J (2008) Psoriasis Vulgaris lesions contain discrete populations of Th1 and Th17 T Cells. *J Invest Dermatol*; 128:1207-11.
- Mancia G, De Backer G, Dominiczak A, et al (2007) Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*; 25:1105-87.
- Manuel O, Kumar D (2008) QuantiFERON-TB Gold assay for the diagnosis of latent tuberculosis infection. *Expert Rev. Mol. Diagn*; 8:247-56.
- Mattei PL, Corey KC, Kimball AB, et al (2014) Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. *J Eur Acad Dermatol Venereol*; 28 (3): 333-7.
- Moll JM and Wright V (1973) Psoriatic arthritis. *Semin Arthritis Rheum*; 3(1):55-78.
- Mrowietz U, Kragballe K, Reich K, et al (2011) Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res*. 303(1):1-10.

Navarini AA, Poulin Y, Gu Y, et al (2012) Adalimumab treatment for moderate to severe psoriasis substantially improves PASI scores as analyzed by body region and individual PASI component: Subanalysis from the CHAMPION study. *J Invest Dermatol*; 132:S85–96.

Naldi L and Mercuri SR (2010) Epidemiology of comorbidities in psoriasis. *Dermatol Ther*; 23(2):114-8.

Nestle FO, Kaplan D, Barker J (2009) Psoriasis. *N Engl J Med*; 361:496-509.

O'Neill P and Kelly P (1996) Postal questionnaire study of disability in the community associated with psoriasis. *BMJ*; 313: 919–21.

Patel DD, Lee DM, Kolbinger F, et al (2013) Effect of IL-17A blockade with secukinumab in autoimmune diseases. *Ann Rheum Dis*. 72:ii116–ii123.

Pathirana D, Ormerod AD, Saiag P, et al (2009) European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol*; 23 Suppl 2:1-70.

Paul C, Gallini A, Maza A, et al (2011) Evidence-based recommendations on conventional systemic treatments in psoriasis: systematic review and expert opinion of a panel of dermatologists. *J Eur Acad Dermatol Venereol*; May 25, Suppl 2:2-11.

Paul C, Reich K, Gottlieb AB, et al (2014) Secukinumab improves hand, foot and nail lesions in moderate-to-severe plaque psoriasis: subanalysis of a randomized, double-blind, placebo-controlled, regimen-finding phase 2 trial. *J Eur Acad Dermatol Venereol*; 28(12):1670-5.

Reich K (2012) The concept of psoriasis as a systemic inflammation: implications for disease management. *J Eur Acad Dermatol Venereol*; 26 (Suppl 2): 3-11.

Reich K, Papp KA, Matheson RT, et al (2015) Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. *Exp Dermatol*; 24(7):529-35.

Revicki DA, Willian MK, Menter A, et al (2007) Impact of adalimumab treatment on patient-reported outcomes: results from a Phase III clinical trial in patients with moderate to severe plaque psoriasis. *J Dermatolog Treat*; 18(6):341-50.

Revicki DA, Willian MK, Menter A et al (2008) Relationship between clinical response to therapy and health-related quality of life outcomes in patients with moderate to severe plaque psoriasis. *Dermatology*; 216(3):260-70.

Rich P, Sigurgeirsson B, Thaci D, et al (2013) Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase II regimen-finding study. *Br J Dermatol*; 168(2): 402-11.

Rønneberg Mehren C, Clemmensen A, Boe-Hansen Dall A, et al (2014) Essential factors influencing health-related-quality of life in psoriasis. *J Drugs Dermatol*; 13(3): 246-50.

Ros S, Puig L, Carascosa JM, et al (2014) Cumulative Life Course Impairment: the imprint of psoriasis on the patient's life. *Acta Dermosifiliograf*; 105(2):128-134.

Summary of Product Characteristics for Secukinumab

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003729/human_med_001832.jsp&mid=WC0b01ac058001d124, accessed 21 Oct 2015.

Shikar R, Willian MK, Okun MM et al (2006) The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. *Health Qual Life Outcomes*; 27(4):71.

Sigurgeirsson B, Kircik L, Nemoto O, et al (2014) Secukinumab improves the signs and symptoms of moderate-to-severe plaque psoriasis in subjects with involvement of hands and/or feet: subanalysis of a randomized, double-blind, placebo-controlled, phase 2 dose-ranging study. *J Eur Acad Dermatol Venereol*; 28 (8): 1127-9.

STEPwise approach to surveillance (STEPS) (2008) Waist Circumference and Waist-Hip Ratio, Report of a WHO Expert Consultation. World Health Organization; 8–11 December.

The EuroQol Group (1990) EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy* 16(3):199-208.

Touw CR, Hakkaart-Van Roijen L, Verboom P et al (2001) Quality of life and clinical outcome in psoriasis patients using intermittent cyclosporine. *Br J Dermatol*; 144(5):967-72.

van Cranenburgh OD, de Korte J, Sprangers MA, et al (2013) Satisfaction with treatment among patients with psoriasis: a web-based survey. *Br J Dermatol*; 169 (2):398–405.

van den Reek JM, van Lüumig PP, Otero ME, et al (2014) Satisfaction of treatment with biologics is high in psoriasis: results from the Bio-CAPTURE network. *Br J Dermatol*; 170 (5):1158-65.

Vender R, Lynde C, Gilbert M, et al (2012) Etanercept improves quality of life outcomes and treatment satisfaction in patients with moderate to severe plaque psoriasis in clinical practice. *J Cutan Med Surg*; 16(6):407-16.

Viswanathan HN, Chau D, Milmont CE, et al (2014) Total skin clearance results in improvements in health-related quality of life and reduced symptom severity among patients with moderate to severe psoriasis. *J Dermatolog Treat*; 31:1-5.

Weisman S, Pollack CR, Gottschalk RW (2003) Psoriasis disease severity measures: comparing efficacy of treatments for severe psoriasis. *J Dermatolog Treat*; 14:158-165.

13 Appendix 1: Clinically notable laboratory values and vital signs

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

No specific action is pre-defined within this protocol to respond to specific abnormal laboratory values, as it will be decided by the Investigator/qualified site staff whether and which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the patient. For additional information please refer to the lab manual.

Liver function and related variables

ALT (SGPT):	> 3 x upper limit of normal (ULN)
AST (SGOT):	> 3 x ULN
Total bilirubin:	> 1.5 x ULN
Alkaline phosphatase:	> 2 x ULN

Renal function and electrolyte variables

Creatinine (serum):	> 1.5 x ULN
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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)
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