NOVARTIS

Global Clinical Development - General Medicine

Secukinumab (AIN457)

Synopsis/Clinical Trial Protocol

CAIN457ADE08 / NCT03440736

A randomized, multicenter 28 week study to compare the efficacy and safety of combining Cosentyx (Secukinumab) (4-weekly, 300 mg s.c.) with a lifestyle intervention to Cosentyx therapy alone in adult patients with moderate to severe plaque-type psoriasis and concomitant metabolic syndrome, followed by a 28 week extension period

METABOLYX

Document type:	Clinical Trial Protocol
EUDRACT number:	2016-001671-79
Version number:	02 (protocol including amendments 1 and 2, track-changes for amendment 2)
Clinical trial phase:	IV
Release date:	05-Sep-2018

Clinical Trial Protocol Template Version 3.2 (July 2016)

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
AHA	American Heart Association
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
b.i.d.	twice a day
BMI	Body Mass Index
CFR	US Code of Federal Regulations
CD	Cluster of differentiation
CDS	Core Data Sheet (for marketed drugs)
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTC	Common Terminology Criteria
CTRD	Clinical Trial Results Database
CTX	Carboxy-terminal collagen crosslinks
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
eSource	Electronic Source
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HDL	high-density lipoprotein
HOMA-IR	Homeostatic model assessment for insulin resistance
hsCRP	high-sensitivity C-reactive Protein
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDF	International Diabetes Federation
IEC	Independent Ethics Committee
IL	Interleukin
IL-1Ra	IL-1 receptor antagonist
IL-18bp	IL-18 binding protein
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDL	low-density lipoprotein
LFT	Liver function test
M30 assay	Keratin 18 fragments that contain the M30 epitope
MedDRA	Medical dictionary for regulatory activities
NAFLD	Non-alcoholic fatty liver disease
NHLBI	National Heart, Lung and Blood Institute

NT-proBNP	N-terminal Brain Natriuretic Peptide
PC	Personal Computer
P1NP	Procollagen type 1 amino-terminal propeptide
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	once a day
OPG	Osteoprotegerin
p.o.	oral(ly)
RANKL	Receptor activator of nuclear factor kappa B ligand
sThy-1	soluble Thy-1
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
TNF	Tumor necrosis factor
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date

Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	*CAIN457ADE08*
Full Title	*A randomized, multicenter 28 week study to compare the efficacy and safety of combining Cosentyx (Secukinumab) (4-weekly, 300 mg s.c.) with a lifestyle intervention to Cosentyx therapy alone in adult patients with moderate to severe plaque-type psoriasis and concomitant metabolic syndrome, followed by a 28 week extension period*
Brief title	*Comparison of Secukinumab 300 mg combined with a lifestyle intervention to Secukinumab alone for the treatment of moderate to severe psoriasis patients with concomitant metabolic syndrome*
Sponsor and Clinical Phase	*Novartis, Phase IV*
Investigation type	*Drug in combination with behavioral change*
Study type	*Interventional*
Purpose and rationale	*Around 40% of moderate to severe psoriasis patients are affected by concomitant metabolic syndrome, making it one of the clinically most relevant comorbidities (Love et al., 2011). Psoriasis as well as the metabolic syndrome are both characterized by a state of low-grade systemic inflammation (e.g. in the skin, joints, adipose tissue, liver or vascular endothelium). This shared pathophysiology makes systemic inflammation an attractive target for the treatment of both diseases. Secukinumab as well as lifestyle intervention are able to reduce systemic inflammation.* *This trial is designed to answer the question whether the combination of Secukinumab with lifestyle intervention can primarily improve skin symptoms and secondly cardiometabolic status more than Secukinumab alone in psoriasis patients with concomitant metabolic syndrome by targeting the shared pathophysiology behind both diseases, which is systemic inflammation.*
Primary Objective(s)	*The primary objective of the study is to demonstrate that the combination of Secukinumab with lifestyle intervention results in higher psoriasis treatment efficacy compared to Secukinumab alone in psoriasis patients with concomitant metabolic syndrome.*
Secondary Objectives	*Objective 1: To explore treatment efficacy of Secukinumab combined with lifestyle intervention in comparison to Secukinumab alone.*

	Objective 2: To evaluate the effect of Secukinumab combined with lifestyle intervention in comparison to Secukinumab alone on systemic inflammation. *Objective 3: To evaluate the effect of Secukinumab combined with lifestyle intervention in comparison to Secukinumab alone on glucose metabolism.* *Objective 4: To evaluate the effect of Secukinumab combined with lifestyle intervention in comparison to Secukinumab alone on lipid metabolism.* *Objective 5: To evaluate the effect of Secukinumab combined with lifestyle intervention in comparison to Secukinumab alone on body weight.* *Objective 6: To evaluate the effect of Secukinumab combined with lifestyle intervention in comparison to Secukinumab alone on systolic and diastolic blood pressure.* *Objective 7: To evaluate the effect of Secukinumab combined with lifestyle intervention in comparison to Secukinumab alone on health-related quality of life and mental well-being.*
Study design	*This study is a randomized, multi-center, open label, parallel group, active comparator-controlled study with a duration of 28 weeks and a 28 week extension phase.*
Population	*This study is planned to enroll approximately 760 patients in Germany with moderate to severe plaque-type psoriasis and concomitant metabolic syndrome, aged ≥18 years.*
Key Inclusion criteria	*Key inclusion criteria are:* 1. *Written informed consent must be obtained before any assessment is performed.* 2. *Men or women of at least 18 years of age at the time of screening.* 3. *Patients with moderate to severe plaque-type psoriasis who are candidates for systemic therapy.* 4. *Fulfillment of metabolic syndrome diagnosis criteria (see section 4.1 for details) at screening visit.* 5. *Willingness and motivation to actively participate in the lifestyle intervention, which means patients need to be willing to increase physical activity and to change dietary habits in order to achieve weight loss.*
Key Exclusion criteria	*Key exclusion criteria are:* 1. *Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis) at screening.*

	2. *Previous exposure to Secukinumab or any other biologic drug directly targeting IL17A or the IL17A receptor (e.g. Brodalumab, Ixekizumab).* 3. *History of hypersensitivity to Secukinumab, trehalose-dihydrate, L-histidine, L-histidinhydrochloride-monohydrate, L-methionine, polysorbate 80, water for injection, or to substances of similar chemical classes.* 4. *Diagnosis of type 1 diabetes.* 5. *Significant, progressive or uncontrolled medical problems at baseline which according to the opinion of the Investigator render the subject unsuitable for the trial - also in regard to participation in the lifestyle intervention - or put the subject at increased risk when participating in the trial.*
Study treatment	• *Secukinumab 300 mg s.c.* • *Secukinumab 300 mg s.c. in combination with a lifestyle intervention*
Efficacy assessments	*Key efficacy assessments are:* • *PASI score* • *Body weight* • *Waist and hip circumference* • *Systolic and diastolic blood pressure* • *Biomarkers of glucose and lipid metabolism as well as systemic inflammation: HbA1c, fructosamine, fasting plasma glucose, total cholesterol, LDL, HDL, triglycerides, hsCRP*
Key safety assessments	*Key safety assessments are:* • *Adverse event monitoring* • *Physical examination* • *Monitoring of laboratory markers in blood and urine*
Other assessments	*Other assessments include:* • *Patient reported outcomes: DLQI, WHO-5, self-assessed itch, pain and scaling*
Data analysis	*The null hypothesis to be rejected is that the odds of response at Week 28 are equal in both treatment groups. The corresponding alternative hypothesis is that the odds of response at Week 28 are higher under Secukinumab combined with lifestyle intervention compared to Secukinumab alone. The primary analysis will be*

	performed comparing treatments with respect to the primary efficacy variable in a logistic regression model with the factors treatment, center and covariate baseline PASI. The odds ratio and its 95% confidence interval (CI) and p-value will be given. The null hypothesis of equal odds will be rejected if the 2-sided p-value from the logistic regression model for the factor "treatment" is < 0.05; however, superiority of Secukinumab combined with lifestyle intervention will be claimed only if the direction is correct, i.e. if the odds of response are larger under Secukinumab combined with lifestyle intervention.
Key words	*plaque-type psoriasis, metabolic syndrome, Secukinumab, lifestyle intervention, systemic inflammation, metabolism*

Amendment 1

The original protocol is amended in order to align details of the protocol with the patient documents of the lifestyle intervention program ("Lesebuch") and in order to complement the protocol with a few details that make the study procedure more clear:

- Section 5.5.3.2: Additional explanation about the time point (visit 2) when patients in arm B receive the materials which are part of the lifestyle intervention
- Section 6.5.4.1: Two laboratory markers are additionally captured at visit 1.
- Section 6: Additional explanatory footnote for table 6-1.
- Section 6.4.5: Waist circumference measurement method is adapted in order to align it with the patient documents of the lifestyle intervention program ("Lesebuch").

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

All protocol changes which are part of this amendment are non-substantial.

Amendment 2

The protocol is being amended in order to incorporate a biomarker sub-study. Moreover, regulations of study treatment discontinuations are being improved, minor inconsistencies are being corrected and clarifications are being added.

- The interaction of psoriasis and its major comorbidity, metabolic syndrome, is well established on an epidemiologic level, showing that more than 40% of psoriasis patients are affected by concomitant metabolic syndrome (Love et al., 2011). On the other hand, the understanding of the detailed molecular mechanisms underlying this interaction is still poor. Low-grade systemic inflammatory processes are thought to be a "common root" and driving force in the pathophysiology of both diseases. Furthermore, other diseases may also be associated with psoriasis and concomitant metabolic syndrome, including osteoporosis and non-alcoholic fatty liver disease. The purpose of this biomarker sub-study is to investigate markers that are implicated in the molecular mechanism of these diseases in subjects with psoriasis and metabolic syndrome in order to better understand their individual contributions as well as their interplay before and during treatment with Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone. **The analyzed biomarkers will include but will not be limited to those linked to lipid, glucose, muscle and bone metabolism, liver fibrosis and steatosis, heart failure, as well as to inflammatory processes.** Due to logistic challenges, not all study sites will be able to participate in the sub-study. It is planned to conduct the sub-study in a subgroup of 100 patients to be recruited in participating sites; 50 treated with Secukinumab and lifestyle intervention and 50 treated with Secukinumab alone. At baseline (week 0), week 16 and week 28 the following markers will be assessed: Free fatty acid serum profile, soluble Thy-1 (sThy-1), adiponectin, leptin, insulin, homeostatic model assessment for insulin resistance (HOMA-IR), proinsulin, interleukin (IL-) 6, tumor necrosis factor (TNF-) alpha, keratin 18 fragments that contain the M30 epitope (M30 assay), IL-1 beta, IL-1 receptor antagonist (IL-1Ra), IL-18, IL-18 binding protein (IL-18bp), procollagen type 1 amino-terminal propeptide (P1NP), carboxy-terminal collagen crosslinks (CTX), receptor activator of nuclear factor kappa B ligand (RANKL), osteoprotegerin (OPG), sclerostin, N-terminal brain natriuretic peptide (NT-proBNP), cluster of differentiation (CD) 154, and a 30-panel multiplex inflammatory cytokine and chemokines panel. The additional risks of participating in the biomarker sub-study are those of blood sampling. Blood sampling will occur at time points where standard blood sampling is scheduled as well, and will **not** require additional venipuncture. **Participation in the sub-study does not negatively affect the overall risk-benefit ratio for participation in the study**. Patients eligible for inclusion in the biomarker sub-study will be recruited at study sites participating in the biomarker sub-study. Written informed consent for the biomarker sub-study must be obtained before any assessment for the biomarker sub-study is performed. The markers will be assessed centrally. Clinically significant abnormal laboratory values will also be assessed by the investigator for adverse event reporting for the following parameters of the biomarker sub-study: Adiponectin,

leptin, insulin, HOMA-IR, proinsulin, IL-6, TNF-alpha, M30 assay, NT-proBNP. Endpoints of the biomarker sub-study will be analyzed using an MMRM-model as described in section 9.5.1. Descriptions of the biomarker sub-study have been added to the sections 2, 3.1, 3.6, 4.1, 6, 6.6.5, 7.1, 9.5.6, and 9.6.

- Section 5.6.2 and table 5-1: After study treatment discontinuation (i.e. discontinuation of secukinumab, lifestyle intervention or both) the patient will now continue to attend regular study visits as per visit schedule and all assessments will be performed as planned. If one study treatment is discontinued (i.e. secukinumab or lifestyle intervention) this should not lead to discontinuation of the other, unless there is a reason for discontinuation of the other. If a study treatment is discontinued, adequate replacement for this treatment may be sought outside of the study despite continued study participation.
- Table 6-1: Clarification that physical examination and drug accounting will only be performed at unscheduled visits, if necessary as determined by the treating physician.
- Section 6.2.2: Clarification that topical therapies are only collected for the last 24 month prior to signing the informed consent.
- Section 6.5.4.3.: Clarification that urine microscopy assessment, if needed, will be performed locally and correction of parameters assessed with the dipstick measurement.
- Section 9.5.1: Clarification that PASI assessments will also be performed at weeks 1, 2 and 3 and addition of missing secondary endpoints.
- Section 9.5.2.2: Change of wording from serum chemistry to clinical chemistry to align with the rest of the protocol.
- The list of abbreviations has been updated.

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

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities (HA). The changes described in this amended protocol require IRB/IEC and HA approval prior to implementation.

1 Introduction

1.1 Background

Psoriasis is a chronic relapsing disease of the skin characterized by variable clinical features. The lesions are classified as erythemato-squamous, which indicates that both the vasculature (erythema) and the epidermis (increased scale formation) are involved (Christophers et al 2003, Griffiths et al 2007). Plaque-type psoriasis (also called plaque or chronic plaque psoriasis) is the most frequent clinical presentation and therefore, also called psoriasis vulgaris. The erythematous plaques are well defined with sharp borders. In approximately one-third of patients, more than 10% of the body is covered, and this is termed moderate to severe psoriasis. Treatment of moderate to severe psoriasis is based on phototherapy, systemic treatment (e.g. Methotrexate, cyclosporine, acitretin) and biologics like tumor necrosis factor alpha (TNFα) - inhibitors, anti-IL 12/23-antibodies or anti-IL17-antibodies.

Secukinumab (AIN457) is a recombinant high-affinity fully human monoclonal anti-human IL17A antibody of the immunoglobulin (Ig) G1/κ-class. Secukinumab binds to human IL17A and neutralizes the bioactivity of this cytokine. IL-17A is the central cytokine of a newly defined subset of inflammatory T cells, the Th17 cells which, in several animal models, are pivotal in multiple autoimmune and inflammatory processes. IL17A is mainly produced by memory effector CD4+ and CD8+ T lymphocytes and is being recognized as one of the principal pro-inflammatory cytokines in immune mediated inflammatory diseases like Psoriasis. Its neutralization targets the underlying pathophysiology of Psoriasis, and as a consequence is able to provide relief of psoriatic symptoms. Secukinumab has been shown to be superior to other biologics such as the TNF-α antagonist Etanercept (Langley et al 2014) and the IL-12/-23 antagonist Ustekinumab (Thaci et al., 2015) in clearing skin of subjects with moderate to severe psoriasis with a comparable safety profile. Secukinumab (Cosentyx®) was approved in 2014 in Japan, and 2015 in USA, EU, Switzerland, and other countries for the treatment of moderate to severe plaque psoriasis in adults with a recommended dose of 300 mg administered as two subcutaneous injections of 150 mg.

Psoriasis is today understood as a systemic disease causing a state of systemic low-grade inflammation affecting more tissues than just the skin (Reich, 2012; Ryan et al., 2015).

Psoriasis is associated with a range of comorbidities, among which the metabolic syndrome plays a central role, affecting more than 40% of the psoriasis patient population (Love et al., 2011). The metabolic syndrome is defined by a cluster of interconnected components which are insulin resistance, obesity, dyslipidemia and elevated blood pressure, resulting in elevated risk for development of type 2 diabetes, coronary heart disease or non-alcoholic fatty liver disease (NAFLD) (Alberti et al., 2009; Kassi et al., 2011). Insulin resistance can be regarded as a key factor, promoting the other components (Kassi et al., 2011). All individual components of the metabolic syndrome show elevated prevalence in psoriasis patients, with odds ratios around 2 compared to a healthy control population (Augustin et al., 2010).

Besides the above mentioned strong epidemiologic association between psoriasis and the metabolic syndrome, these two diseases show a clear pathophysiologic overlap in form of systemic low-grade inflammation, which appears to serve as a “common root” of both diseases

and potentially is the reason for their close association (Takahashi et al., 2012; Toussirot et al., 2014): Metabolic syndrome and foremost its two key components insulin resistance and obesity, are today understood as a state of systemic low-grade inflammation, similar to the understanding of psoriasis as a systemic inflammatory disease. During the last two decades a still growing body of evidence has shown clear association between inflammation and cardiometabolic disorders. The central role of TNFα or IL-1ß in the development of insulin resistance, ß-cell failure, vascular inflammation and atherosclerosis are just a few examples, the emerging role of hsCRP as a predictive marker for cardiovascular events another one. Adipose tissue, liver tissue or the vascular endothelium are typical examples for sites of inflammation in obesity/ metabolic syndrome and low-grade systemic inflammation is considered to be the key link between obesity and its related comorbidities (Shoelson et al., 2009; Esser et al., 2014). Adipose tissue secreted hormones - so called adipokines - have systemic immunologic impact, including influence on psoriatic skin, some of pro-inflammatory (e.g. visfatin, resistin) others of anti-inflammatory character (adiponectin) (Gerdes et al., 2011). Adipokine secretion is heavily dysregulated in psoriasis patients and their pathophysiologic role receives growing attention including their role as mediators of cardiometabolic comorbidities in psoriasis and obesity (Coimbra et al., 2016).

Insulin resistance, a key criterion of the metabolic syndrome diagnosis, is also a key component of psoriasis pathophysiology, reflected in the so called “psoriatic march” concept, which describes the inflammation-driven expansion of insulin resistance throughout the vascular endothelium and psoriatic skin lesions in psoriasis patients (Boehncke et al., 2007; Boehncke et al., 2011).

Considering the interconnected pathophysiology of both diseases it seems highly promissing to try shared approaches for the treatment of psoriasis and its major comorbidity, the metabolic syndrome, based on a deeper understanding of the common mechanism behind these diseases, which is systemic inflammation.

Lifestyle intervention is the long-established gold standard for the treatment of obesity and metabolic syndrome. Several clinical studies have proven the ability of lifestyle interventions to induce weight loss and achieve cardiometabolic benefits, which are mainly improvement of glucose and lipid metabolism, as well as reductions in systolic and diastolic blood pressure (Yamaoka et al., 2012). Weight loss and the above mentioned cardiometabolic improvements are associated with preventive effects, such as cardiovascular risk reduction and lowering of the risk of progression from prediabetes to type 2 diabetes. These improvements would be of high benefit to the psoriasis patient population, considering their elevated cardiovascular risk profile (Reich, 2012).

Even more important for the present study, lifestyle interventions (weight loss and increased physical activity) have shown positive effects in the treatment of psoriasis: Weight reductions are associated with improvements in Psoriasis Area and Severity Index (PASI) scores (Debbaneh et al., 2014) and pilot studies have shown improvements of response to conventional systemics or biologics when combined with lifestyle interventions (Gisondi et al., 2008; Al-Mutairi et al., 2014). Weight reduction and increased physical activity are associated with suppression of systemic inflammation (Petelin et al., 2014). Furthermore a recent study by Coimbra et al. has shown that concomitant metabolic syndrome in psoriasis patients inhibits the suppressive effects of psoriasis therapy on systemic inflammation and IL17-signalling, thereby

reducing the length of remission (Coimbra et al., 2016). This indicates that tissue inflammation present in metabolic syndrome, especially adipose or liver tissue inflammation, can serve as a secondary source of systemic inflammation after successful control of skin inflammation by psoriasis therapy. This gives us another reason to target systemic inflammation caused by metabolic syndrome in addition to skin inflammation. Clinical studies have shown the reversibility of adipose and liver tissue inflammation present in obesity: Weight loss has been shown to reduce immune cell infiltration in adipose and liver tissue (Cancello et al., 2005; Schmitz et al., 2016).

Blockade of IL-17A with Secukinumab is also known to control systemic inflammation, shown for example by hsCRP suppression under Secukinumab therapy (Novartis data on file).

From a clinical perspective the appropriate treatment of cardiometabolic comorbidities in psoriasis patients by the use of a professional concomitant lifestyle modification is potentially of high relevance to treating dermatologists, as these comorbidities affect around 40% of the patient population, are often difficult to treat and are key determinants of patients´ cardiovascular risk profile.

It is of further interest in this context that several current systemic treatment options for psoriasis have well-described negative side effects on psoriasis´ cardiometabolic status (Gisondi et al., 2015). Methotrexate for example should be prescribed with caution in the presence of obesity, diabetes, NAFLD and reduced kidney function because of increased risk of liver fibrosis and drug toxicity. Cyclosporine can induce or worsen arterial hypertension, increase insulin resistance and worsen dyslipidemia and hyperuricemia. Acitretin favors hypertriglyceridemia and hypercholesterinemia. In contrast to that, no negative metabolic side effects are known for Secukinumab.

Taken together, further improvement of efficacy and positive cardiometabolic effects of Secukinumab in combination with lifestyle intervention would be an innovative approach enabling physicians and patients to achieve both treatment goals with one integrated treatment concept, well-controlled psoriasis and cardiovascular risk factor control.

1.2 Purpose

This trial is designed to answer the question whether the combination of Secukinumab with lifestyle intervention can primarily improve skin symptoms and secondly cardiometabolic status more than Secukinumab alone in psoriasis patients with concomitant metabolic syndrome by dual targeting of the shared pathophysiology behind both diseases, which is systemic inflammation.

2 Study objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that the combination of Secukinumab (300 mg, 4-weekly s.c.) with lifestyle intervention results in higher psoriasis treatment efficacy than Secukinumab alone in psoriasis patients with concomitant metabolic syndrome	• Percentage of patients achieving PASI90 at week 28 in both randomized treatment arms, Secukinumab alone and Secukinumab combined with lifestyle intervention
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To explore treatment efficacy of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone	• PASI75, 90 and 100 as well as absolute PASI scores in both treatment arms at week 1, 2, 3, 4, 8, 12, 16, 20, 24 and 28
• To evaluate the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on systemic inflammation	• hsCRP in both treatment arms throughout the duration of the core study
• To evaluate the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on glucose metabolism	• HbA1c, fructosamine and fasting plasma glucose in both treatment arms throughout the duration of the core study
• To evaluate the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on lipid metabolism	• Total cholesterol, LDL, HDL and triglycerides in both treatment arms throughout the duration of the core study
• To evaluate the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on body weight and waist circumference	• Waist circumference, body weight and BMI in both treatment arms throughout the duration of the core study
• To evaluate the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on systolic and diastolic blood pressure	• Systolic and diastolic blood pressure in both treatment arms throughout the duration of the core study
• To evaluate the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with	• Absolute DLQI, relative change of DLQI, proportion of patients with

Objective(s)	Endpoint(s)
lifestyle intervention in comparison to Secukinumab alone on health-related quality of life, itch, pain and scaling as well as mental well-being	DLQI 0/1, absolute WHO-5, relative change in WHO-5, absolute self-assessed itch, pain, scaling, relative change in self-assessed itch, pain, scaling in both treatment arms throughout the duration of the core study

Objective(s)	Endpoint(s)
• To explore the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on biomarkers including but not limited to those linked to lipid, glucose, muscle and bone metabolism, liver fibrosis/steatosis, heart injury, as well as to inflammatory processes in a subgroup of 100 patients (50 treated with secukinumab and lifestyle intervention and 50 treated with secukinumab alone)	• At baseline (week 0), week 16 and week 28 the following markers will be assessed: Free fatty acid serum profile, sThy-1, adiponectin, leptin, insulin, HOMA-IR, proinsulin, IL-6, TNF-alpha, M30 assay, IL-1 beta, IL-1Ra, IL-18, IL-18bp, P1NP, CTX, RANKL, OPG, sclerostin, NT-proBNP, CD154, and a 30-panel multiplex inflammatory cytokine and chemokines panel

3 Investigational plan

3.1 Study design

Figure 3-1 Study design

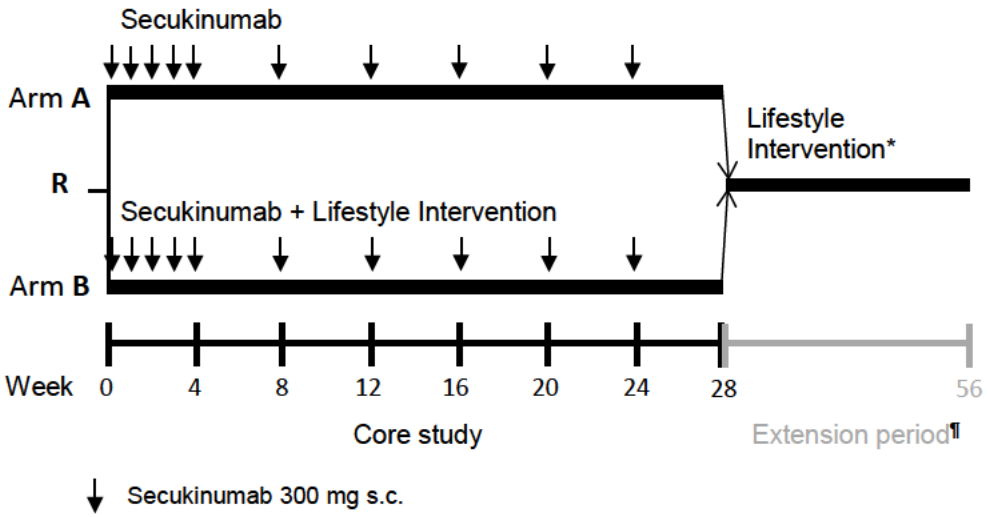


Fig. 3-1: Study Design: **R** Randomization, *During the extension period lifestyle intervention can be continued by patients who have been in arm B during the core study or it can be started by patients who have been in arm A. Participation in the lifestyle intervention during the extension period is **not** mandatory. ¶Participation in the extension period itself is mandatory. Psoriasis treatment during the extension period can be chosen freely by the Investigator. No study drug is supplied during the extension period.

This study is designed as a randomized, open-label, parallel-group, active comparator-controlled trial with two treatment arms. The design is shown in Figure 3-1.

Core study: After providing informed consent patients will be screened for eligibility for a period of 1-4 weeks prior to inclusion into the study. If eligible, patients will then be randomized to one of the two treatment arms, which are the following:

- **Arm A**: Patients in arm A receive a regular induction followed by 4-weekly maintenance treatment with Secukinumab 300 mg s.c. until week 28, where they complete the core study. The last Secukinumab injection is performed at week 24.
- **Arm B**: Patients in arm B receive a regular induction followed by 4-weekly maintenance treatment with Secukinumab 300 mg s.c. until week 28. The last Secukinumab injection is performed at week 24. **In addition to Secukinumab treatment patients in arm B participate in a lifestyle intervention program**.

A biomarker sub-study will be conducted during the core study in a subgroup of 100 patients (50 from each treatment arm).

The core study ends at week 28.

Extension period: After 28 weeks the study continues with an extension period, during which lifestyle intervention is offered to all patients, irrespective of their prior treatment arm. This means that patients of arm B, who are willing to, can continue their previously started lifestyle intervention program and patients of arm A, who are willing to, can start the lifestyle intervention program at the beginning of the extension period. **All patients, irrespective of their decision whether to start/ continue lifestyle intervention or not, have to participate in the extension period and visit their dermatologic study center for scheduled visits**. The extension period ends at week 56, where all patients complete the study. There will be no study drug supply during the extension period. The treating physician can chose psoriasis therapy freely according to his discretion.

3.2 Rationale for study design

This study design was chosen in order to be able to demonstrate that the combination of Secukinumab (300 mg, 4-weekly s.c.) with lifestyle intervention results in higher psoriasis treatment efficacy compared to Secukinumab alone in psoriasis patients with concomitant metabolic syndrome. Therefore a randomized study set up with two treatment arms was chosen, arm B, where patients receive Secukinumab treatment combined with lifestyle intervention and arm A as active comparator control group, where patients receive Secukinumab alone.

The design enables assessment of the <u>additional</u> effects of concomitant lifestyle intervention on psoriasis treatment efficacy of Secukinumab as well as on metabolic status of the patients.

The open-label design is a consequence of the lifestyle intervention, which would be very difficult to blind. This might theoretically lead to a certain bias concerning psoriasis severity assessments (PASI), as investigators could expect patients receiving additional lifestyle intervention to show stronger improvements. On the other hand lifestyle intervention is no drug therapy and is not established as therapeutic intervention in psoriasis therapy, which limits the bias. Furthermore the study includes an extension period, which offers lifestyle intervention to

all patients and which includes a final PASI assessment at the end of the extension period, thereby further limiting the bias. Other, secondary objectives, like improvement of glucose and lipid metabolism, reduction of blood pressure, weight loss or changes in biomarker levels are based on laboratory parameters (HbA1c, lipid panel, biomarkers) or technical measurements (blood pressure, body weight), where the influence of a potential bias is highly limited.

The extension period was designed for five reasons: First it enables the assessment of long-term sustainability of weight loss and lifestyle changes induced by the lifestyle intervention and second it helps to answer the question whether continued lifestyle intervention is necessary to maintain weight loss and other beneficial effects. Third it offers motivated patients of arm B the chance to receive continued support. Fourth it compensates for the disadvantage patients of arm A had, who were not allowed to participate in lifestyle intervention during the core study. And the fifth reason is that it helps to answer the question whether patients still benefit from a lifestyle intervention even if a systemic therapy has been initiated 28 weeks ago.

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 trial program. The 300 mg s.c. dose of Secukinumab 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). Furthermore 300 mg is the approved dosing and was therefore selected for this study. The dose interval for the initial treatment period (i.e. once every week for the first 4 weeks, followed by once every 4 weeks until Week 24) has been selected because the phase 3 clinical trial program demonstrated a strong efficacy response to treatment at this dose interval and because this is the approved dose interval for Secukinumab.

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 studies, which showed the use of PFS was safe and well tolerated. Self-injection with the PFS, following the approved and utilized instructions for use, showed no significant safety hazards and was found to be acceptable to study participants and to the competent authorities for other Secukinumab studies (CAIN457A2312 and CAIN457A3301).

Secukinumab 300 mg s.c. treatment is combined with a lifestyle intervention. Lifestyle intervention, consisting of diet modification and increased physical activity, is a long-established therapy and gold standard for the treatment of metabolic syndrome. Furthermore weight loss and increased physical activity were shown to reduce systemic inflammation, which is, as described in section 1, a shared pathophysiological process of psoriasis and metabolic syndrome. Therefore synergies of lifestyle intervention and Secukinumab therapy can be expected, as IL17A blockade with Secukinumab is also known to control systemic inflammation, shown for example by hsCRP suppression under Secukinumab therapy.

Dual targeting of systemic inflammation by Secukinumab and lifestyle intervention is expected to improve skin symptoms more than Secukinumab alone and rearrange deteriorated metabolic status at the same time.

The duration of the combined treatment was chosen in alignment with the kinetics of the lifestyle intervention. Optimal weight loss during lifestyle intervention can be expected after approximately 3-4 month. The extent of weight loss is expected to correlate to a certain degree with the reduction of systemic inflammation and thereby with psoriasis status. Thus the duration of 28 weeks seems optimal, as it can be expected that patients have already reached maximum weight loss and have maintained it for a while. In order to be able to assess the long-term sustainability of this intervention the study contains an extension period with metabolic and psoriasis assessment after 56 weeks.

3.4 Rationale for choice of comparator

Secukinumab 300 mg without concomitant lifestyle intervention was chosen as comparator because the study´s purpose is to assess the additional effect of lifestyle intervention on Secukinumab´s treatment efficacy. Therefore Secukinumab treatment alone is the optimal comparator.

3.5 Purpose and timing of analyses

A first analysis of the core study (primary, secondary [redacted] endpoints related to the core study) will be performed after all subjects have completed the core study. [redacted]

The two analyses will be reported in separate clinical study reports.

3.6 Risks and benefits

All patients in this study receive Secukinumab treatment. Secukinumab has a substantial clinical benefit and a favorable safety profile which were thoroughly analyzed in the pivotal clinical trials which resulted in marketing approval of Secukinumab for moderate-to-severe plaque psoriasis, active psoriatic arthritis, and active ankylosing spondylitis.

As of 25-June-2017, more than 23,000 healthy subjects and patients have been enrolled in the Secukinumab Novartis-sponsored clinical trial program. Of these approximately 20,000 have received at least one dose of Secukinumab. Approximately 4000 patients with moderate to severe plaque psoriasis were included in studies in the psoriasis registration program. The Phase 3 development program 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. The majority of patients treated with this dose achieved clear to almost clear skin, as PASI90 response and Investigator Global Assessment modified (IGA mod) 2011 0 or 1 response. More patients treated with 300 mg achieved clear/almost clear skin compared with the 150 mg dose, placebo, or with the active comparator Etanercept, across all pivotal studies, and for all time points between Week 12 and Week 52. In addition, 3 year data from the extension study CAINA2304E1 showed sustained PASI75, 90 and 100 responses for both, the 150 mg and 300 mg doses of Secukinumab. However PASI75, 90 and 100 responses were higher for the 300 mg dose at all time points.

From a safety perspective, Secukinumab was well tolerated in all indications studied. Secukinumab doses of 75mg, 150 mg and 300 mg s.c. were comparable in terms of safety across

all indications evaluated. Secukinumab-specific treatment-emergent Anti-Drug Antibodies (ADA) were detected across the Phase 2 and 3 program in a minimal number of patients (0.7%), who were ADA-negative prior to Secukinumab exposure. Treatment-emergent ADAs were not associated with a loss of efficacy or alteration of pharmacokinetics in patients with assessable data. No severe or serious hypersensitivity reactions or administration reactions were reported in any patients with treatment-emergent ADAs. Long term safety data for up to 3 years did not reveal any new and unexpected adverse events.
Secukinumab has the potential to increase the risk of infections. In clinical studies, most of the infections were of mild or moderate intensity. No increased susceptibility to tuberculosis was reported from clinical studies. Exacerbations of Crohn's disease, in some cases serious, were observed in clinical studies in both patients receiving Secukinumab and placebo. In clinical studies, urticaria and rare cases of anaphylactic reactions have been observed in patients receiving Secukinumab. There are no adequate data from the use of Secukinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development. It is not known whether Secukinumab is excreted in human milk. The effect of Secukinumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility. The Investigator's Brochure (IB) provides a more detailed review of the pre-clinical and clinical information on Secukinumab.

In summary, the overall benefits of treatment with Secukinumab outweigh the risks.

Half of the patients in the present study are randomized to receive concomitant lifestyle intervention in addition to Secukinumab therapy. Lifestyle intervention is the gold standard for the treatment of obesity and other components of the metabolic syndrome. Lifestyle interventions have been proven safe and effective in several studies (Knowler et al. 2002, Tuomilehto et al. 2001, Kulzer et al. 2014). A systematic review of 11 randomized controlled studies of lifestyle interventions shows their ability to induce weight loss and cardiometabolic benefits, which are mainly improvement of glucose and lipid metabolism, as well as reductions in systolic and diastolic blood pressure (Yamaoka et al., 2012). Weight loss and above mentioned cardiometabolic improvements are associated with preventive effects, meaning lower cardiovascular risk and lower risk of progression from prediabetes to type 2 diabetes. The targeted weight loss is >5% of baseline weight, as this extent of weight loss was previously shown to be sufficient to achieve cardiometabolic benefits and associated preventive effects (Lindstrom J, 2006). Furthermore the benefit of weight loss in the treatment of psoriasis was shown in first pilot studies, as mentioned in section 1 (Naldi et al., 2014, Al-Mutairi et al., 2014). The lifestyle intervention applied in this study is based on education about nutrition, metabolism, effects of nutrition and physical activity on metabolic syndrome as well as on active support in weight loss and increased physical activity. Furthermore it includes the use of digital tracking devices. Potential risks of lifestyle intervention can be regarded as minimal. Patients who do not qualify for dietary changes and increased physical activity because of any medical condition, such as cardiac comorbidities (e.g. congestive heart failure), type 1 diabetes, or because any other medical conditions that would put them at risk when participating in the lifestyle intervention, will be excluded from the study, in order to minimize the risk. Furthermore patients with type 2 diabetes who receive insulin-based therapy or sulfonylurea agents/analogues are excluded from the study due to their increased risk for hypoglycemia when combining these medications with changes in diet and physical activity and due to the limited

ability to lose weight under these medications (weight gain is a well-known side effect of insulin and sulfonylurea agents/analogues). Patients with type 2 diabetes receiving other medications, such as DPP4 inhibitors, are allowed to participate in the study, as lifestyle intervention is the guideline-recommended basic therapy for any patient with type 2 diabetes (NVL Therapie des Type-2-Diabetes), and offers benefit for them, which outweighs the potential small risk of hypoglycemia or ketoacidosis in the case of metformin. The treating family physicians of the patients participating in the lifestyle intervention will be notified about the participation in the lifestyle intervention, so they can adequately monitor them and adjust their antidiabetic or antihypertensive medication.

Based on the current knowledge no interactions with negative consequences between Secukinumab therapy and lifestyle intervention can be expected. On the contrary, it is the goal of this study to assess potential positive effects of the combined application. The risk will be further minimized by close clinical and laboratory monitoring of participating patients at all study visit.

The additional risks of participating in the biomarker sub-study are those of blood sampling. Blood sampling will occur at time points where standard blood sampling is scheduled as well, and will not require additional venipuncture. Participation in the sub-study does not negatively affect the overall risk-benefit ratio for participation in the study.

4 Population

The study is conducted in Germany and the study population consists of a representative group of male and female patients (≥18 years old) with moderate to severe plaque-type psoriasis and concomitant metabolic syndrome according to International Diabetes Federation (IDF), American Heart Association (AHA), and National Heart, Lung and Blood Institute (NHLBI) consensus definition from 2009 (Alberti et al., 2009). The goal is to randomize a total of approximately 760 patients in approximately 100 sites in Germany. Considering analyses of prior studies and the inclusion criterion metabolic syndrome, a screening failure of 30 % is expected, making screening of approximately 1100 patients necessary in order to provide the required number of patients.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Men or women of at least 18 years of age at the time of screening.
3. Patients must be able to understand and communicate with the investigator and must be willing and able to comply with all study procedures.
4. Patients with moderate to severe plaque-type psoriasis who are candidates for systemic therapy, diagnosed at least 6 month before randomization and baseline value of
    - PASI > 10 and

- DLQI > 10 and
- Body Surface Area (BSA) affected by plaque-type psoriasis ≥ 10%

5. Fulfillment of Metabolic Syndrome definition (Alberti et al., 2009), which means fulfillment of ≥3 of the following criteria **at screening visit**:
   - **Fasting** (8 hours) plasma glucose ≥ 100 mg/dl or ongoing antidiabetic drug treatment (defined as: metformin, DPP4 inhibitors, GLP1 analogues, SGLT2 inhibitors)
   - Abdominal obesity defined by elevated waist circumference (measured as defined in section 6.4.5): Male: ≥94 cm, female: ≥80 cm (except for patients of Asian, South or Central American ethnicity, for whom the cut off values are: Male: ≥90 cm, female: ≥80 cm)
   - **Fasting** (8 hours) triglycerides ≥ 150 mg/dl or ongoing drug treatment for elevated triglycerides (defined as: fibrates or nicotinic acid).
   - **Fasting** (8 hours) HDL-C < 40 mg/dl in men or < 50 mg/dl in women or ongoing drug treatment for reduced HDL-C (defined as: fibrates, nicotinic acid or statins).
   - **Resting** blood pressure: Systolic blood pressure ≥ 130 and/ or diastolic blood pressure ≥ 85 mmHg (measured as defined in section 6.4.6) or ongoing antihypertensive drug treatment [defined as: ACE inhibitors, beta blockers, angiotensin receptor antagonists (e.g. Valsartan), aldosterone receptor antagonists, diuretics, nitrates, calcium channel blockers (e.g. Verapamil, Nifedipin), Aliskiren, Clonidin, alpha1 receptor antagonists (e.g. Doxazosin), Dihydralazin, Minoxidil, Moxonidin or Methyldopa].
6. Willingness and motivation to actively participate in a lifestyle intervention, which means patients need to be willing to increase physical activity and to change dietary habits.

Patients eligible for inclusion in the biomarker sub-study will be recruited at study sites participating in the biomarker sub-study. Written informed consent for the biomarker sub-study must be obtained before any assessment for the biomarker sub-study is performed.

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.

1. Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis) at screening.
2. Previous exposure to Secukinumab or any other biologic drug directly targeting IL17A or the IL17A receptor (e.g. Brodalumab, Ixekizumab).
3. Exposure to anti-TNF treatment during 1 year prior to baseline.
4. Drug-induced psoriasis (i.e., new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium) at screening.
5. History of hypersensitivity to Secukinumab, trehalose-dihydrate, L-histidine, L-histidinhydrochloride-monohydrate, L-methionine, polysorbate 80, water for injection, or to substances of similar chemical classes.
6. History of latex hypersensitivity.
7. Ongoing participation (including safety follow-up period) in other interventional or non-interventional studies in any dermatological indication
8. Ongoing use of prohibited treatments. Washout periods detailed in the protocol have to be adhered to (Table 5-1). Note: Administration of live vaccines 6 weeks prior to baseline (visit 2) or during the study period is also prohibited.
9. Diagnosis of type 1 diabetes.
10. Patients with diagnosed type 2 diabetes, if they fulfill one or more of the following conditions:
    - uncontrolled type 2 diabetes, meaning HbA1c > 8.0%,
    - pharmacological therapy with one or more of the following agents: Insulin, sulfonylurea agents/analogues, thiazolidinediones/glitazones
11. Insufficiently controlled, severe arterial hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg) with urgent need for therapy initiation or foreseeable need for medication change during the duration of the core study.
12. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations.
13. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
14. Active ongoing inflammatory diseases other than psoriasis and psoriatic arthritis (PsA) that might confound the evaluation of the benefit of Secukinumab therapy.

15. Underlying conditions (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy.
16. Significant, progressive or uncontrolled medical problems at baseline which according to the opinion of the Investigator render the subject unsuitable for the trial - also in regard to participation in the lifestyle intervention - or put the subject at increased risk when participating in the trial (e.g. broken leg, congestive heart failure NYHA III/IV, uncontrolled hypertension with systolic ≥ 160 mmHg and/or diastolic ≥ 95 mmHg, severe uncontrolled asthma)
17. Medical history of myocardial infarction or angina pectoris
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. Serum creatinine level exceeding 2.0 mg/dl (176.8 µmol/L) at screening
20. Total white blood cell (WBC) count < 2,500/µl, or platelets < 100,000/µl or neutrophils < 1,500/µl or hemoglobin < 8.5 g/dl at screening.
21. Active systemic infections during the last two weeks (exception: common cold) prior to baseline (visit 2) or any infection that reoccurs on a regular basis.
22. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold test (QFT) at screening. Subjects with a positive or indeterminate QFT test may participate in the study if full tuberculosis work up (according to local practice/guidelines) was completed within 12 weeks prior to visit 2 and establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then appropriate treatment must have been initiated at least 4 weeks prior to baseline (visit 2) and maintained according to local guidelines.
23. Past medical history record or current infection with HIV, hepatitis B or hepatitis C prior to baseline (visit 2).
24. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks prior to baseline (visit 2); carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
25. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
26. History or evidence of ongoing alcohol or drug abuse, within the last six months before baseline (visit 2).
27. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug for at least 20 weeks after the end of Secukinumab treatment. Basic contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps).
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

During the core study patients in both treatment arms, A and B, receive the same study drug supplied by Novartis and appropriately labeled:

Secukinumab 300 mg, provided as two s.c. injections of 1 ml prefilled syringe (PFS). Each 1 ml syringe contains 150 mg Secukinumab.

5.1.2 Additional treatment

Patients in arm B receive additional treatment in form of a lifestyle intervention.

The lifestyle intervention is based on a structured and standardized program, closely guiding patients with metabolic syndrome with the primary goal to improve their metabolic status and to lose weight. The program and its content is designed by the [redacted] under the

leadership of Prof. Dr. med. [redacted] especially for this trial. It is tailored to the needs of the trial´s patient population and optimized for combination with Secukinumab therapy. Patients are individually and regularly supervised by qualified trainers. They receive standardized education in nutrition, physical activity and metabolism, they learn about effects of nutrition and physical activity and they are consulted how to change their habits, their diet and how to increase their physical activity level. The lifestyle intervention actively enforces patient´s own motivation for lifestyle changes, with the goal to induce long-lasting changes in nutritional and physical activity habits leading to sustained weight reduction and improvement of metabolic status. Patients receive tracking devices, which support patient´s own motivation. The program is conducted in a standardized way, meaning that educational material and teaching is standardized and trainers, who perform the lifestyle intervention, have received standardized instructions (workshop and written information) before they can instruct patients. All trainers have to participate in a workshop conducted by [redacted] to qualify for counseling of the patients. The trainers are also instructed to report (serious) adverse events that are mentioned by the patient during the lifestyle intervention program or that occur during the training within 24 hours to the respective investigator. The investigator will assess whether the event constitutes a non-serious or serious adverse event and report it, if applicable. The main principle of the lifestyle intervention program is based on the programs applied in two milestone trials in the field of lifestyle intervention in patients with metabolic syndrome (Knowler et al., 2002; Tuomilehto et al., 2001). Details of the lifestyle intervention program are given in a separate manual.

5.2 Treatment arms

Core study: The study has two different treatment arms:

- **Arm A**: Patients in arm A receive therapy with Secukinumab 300 mg s.c., which consists of two injections with 150 mg prefilled syringes at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20 and 24 (last injection is performed at week 24)
- **Arm B**: Patients in arm B receive therapy with Secukinumab 300 mg s.c., which consists of two injections with 150 mg prefilled syringes at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20 and 24 (last injection is performed at week 24). **In addition they participate in a lifestyle intervention program.**

Extension period: After 28 weeks the study continues with an extension period, during which lifestyle intervention is offered to all patients, irrespective of their prior treatment arm. This means that patients of arm B, who are willing to, can continue their previously started lifestyle intervention program and patients of arm A, who are willing to, can start the lifestyle intervention program at the beginning of the extension period. The extension period ends at week 56. There will be no study drug supply during the extension period. The treating physician is free to choose suitable psoriasis therapy for each patient.

5.3 Treatment assignment and randomization

Patients will be randomized in a 1:1 ratio to one of the two treatment arms at randomization visit. Randomization will be performed by the use of sealed envelopes. The investigator or his/her delegate will open the sealed envelope after confirming that the patient fulfills all ex- and inclusion criteria. The envelope will assign a randomization number to the patient, which can be used to link the patient to a treatment arm.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

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

At randomization visit an eligible patient will be given the lowest available randomization number. This number assigns the patient to one of the treatment arms. The investigator will enter the randomization number on the case report form (CRF).

5.4 Treatment blinding

Not applicable, as this study has an open label design.

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 in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients/subjects are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). Once assigned to a patient, a patient number will not be reused. If the patient fails to be randomized for any reason, the reason for not being randomized will be entered on the Screening Log. Additional information to be collected on Screening Failures is described in Section 6.1.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance. Due to the open-label design of the study the study drug is not specifically labelled with medication numbers.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

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

5.5.3.2 Handling of additional treatment

Dermatologic study site personnel will instruct patients how to contact their lifestyle intervention trainer in order to participate in the lifestyle intervention program. For patients randomized to receive concomitant lifestyle intervention **it is mandatory to participate in the lifestyle intervention and to show up to the counseling appointments scheduled**. All patient materials which are part of the lifestyle intervention (Lese-/Arbeitsbuch, information flyer, activity tracker, Theraband, scale, tape measure) are given to patients in arm B at randomization visit (study visit 2).

5.5.4 Instructions for prescribing and taking study treatment/ for participating in the lifestyle intervention program

The first study treatment administration will occur at baseline (visit 2) after the inclusion/exclusion criteria have been confirmed and all study scheduled assessments have been performed.

All doses of study treatment are administered at the study site by study site personnel or by the patient himself under the supervision of study site personnel. All study assessments, including blood withdrawal and completion of Patient Reported Outcomes (PROs), i.e. DLQI, should be completed prior to the injection of study treatment. The flow of work and the consecutive steps of assessments including Clinical Outcome Assessments (COA) are given in Section 6.

In single, **exceptional** cases where a visit needs to be skipped e.g. due to business/ working travels of the patient, home administration of study treatment by the patient himself without supervision is allowed at the discretion of the investigator for up to one time per patient between week 8 and week 24. In these cases the investigator is allowed to provide the patient at most one dose of study treatment (2 pre-filled syringes) in advance. Study treatment must be transported in a suitable cooled bag, which will be provided at the study sites. During home administrations subjects are expected to contact the investigator/site staff in case they are experiencing any AE/SAE or have any concerns or are unable for any reason to take the study treatment as prescribed. A visit should be scheduled as close as possible to the time of the per protocol planned visit which had to be skipped. At this visit all assessments of the skipped visit should be performed but no study drug will be administered.

Irrespective of self-administration or administration by study site personnel, the **first** Secukinumab administration at baseline (visit 2) will take place at the study site. In case the patient considers self-administration he must be instructed through the site staff by explaining

the Instructions For Use (IFU) on how to self-inject via the pre-filled syringe. After providing detailed explanations/instructions, subjects will then be asked to raise any questions. Thereafter, they will proceed with self-injection. In case of self-administration the investigator is obliged to make sure that injections are performed correctly and exactly as prescribed. In case of doubt about patient´s ability or willingness to perform injections reliably and correctly the investigator can decide to prohibit self-administration.

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

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

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study.

The lifestyle intervention program has scheduled counseling visits where the patients meet their trainer. These visits are defined in a separate manual. For patients randomized to concomitant lifestyle intervention it is mandatory to participate in the program and to show up for the counseling visits. Participation in the lifestyle intervention counseling visits must be recorded in the eCRF. The investigator should explain to the patient that participation in the program and showing up to all counseling visits is mandatory, necessary for the validity of the study and yields benefit for the patient.

5.5.5 Permitted dose adjustments and interruptions of study treatment/ interruptions of lifestyle intervention

Treatment interruptions and dose adjustments of study treatment are **not** permitted. If a dose was not or incorrectly administered, this deviation must be recorded on the Dosage Administration Record CRF.

The same applies for the lifestyle intervention: Stopping participation (e.g. not showing up to counseling visits) or skipping counseling visits of the program is not permitted. Participation in the lifestyle intervention program must be recorded in the eCRF.

5.5.6 Rescue medication

Use of rescue medication is not permitted in this study.

5.5.7 Concomitant medication

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

after the patient was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies eCRF.

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

Please see table 5-1 for details on prohibited and concomitant medication.

5.5.8 Prohibited medication

Use of the treatments displayed in the below table is NOT allowed during the respective period.

Table 5-1 Prohibited treatments by period (for any indication)

Prohibited treatments during the core study[a, b, g, h]	**Washout period (before baseline, i.e. visit 2)**
Secukinumab and other IL-17 and IL-17 receptor antagonists (e.g. Ixekizumab, Brodalumab)	No prior use allowed
Biologicals targeting TNF (e.g. Etanercept, Adalimumab, Infliximab)	No use **1 year** prior to baseline visit (visit 2) allowed
Alefacept, Briakinumab, Efalizumab, Ustekinumab	6 month
Biological immunomodulating agents other than above	12 weeks
Other systemic immunomodulating treatments (e.g. Methotrexate, cyclosporine A, corticosteroids[c], cyclophosphamide)	4 weeks
Other systemic psoriasis treatments[d] (e.g. retinoids, fumarates, apremilast)	4 weeks
Photochemotherapy (e.g. systemic PUVA, Balneo-PUVA, topical PUVA)	4 weeks
Phototherapy (e.g., UVA, UVB, Balneo-Phototherapy without psoralen derivatives)	2 weeks
Topical treatment that is likely to impact signs and symptoms of psoriasis (vitamin D analogues, Tacrolimus, Pimecrolimus potent corticosteroids, salicylvaseline, salicylic acid, lactic acid, tar, alpha-hydroxy or fruit acids)[e].	2 weeks
Live virus vaccinations***	6 weeks
Any investigational treatment (including anti IL23p19) or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
The following glucose-lowering agents: Insulin, sulfonylurea agents/analogues, thiazolidinediones/glitazones	12 weeks
It is forbidden <u>to start</u> therapy with one of the following medications during the core study[f]:	

Prohibited treatments during the core study[a, b, g, h]	**Washout period (before baseline, i.e. visit 2)**
Cholesterol- or lipid lowering agents(e.g. HMG-CoA-inhibitors/statins, fibrates, nicotinic acid, ezetimibe, colestyramin, colestipol)	
Antihypertensive drugs (e.g. ACE-inhibitors, angiotensin-receptor antagonists, ß-blockers, aldosterone receptor antagonists, diuretics, nitrates, calcium channel blockers (e.g. Verapamil, Nifedipin), Aliskiren, Clonidin, alpha1 receptor antagonists (e.g. Doxazosin), Dihydralazin, Minoxidil, Clonidin, Moxonidin or Methyldopa)	
Glucose-lowering agents (e.g. Metformin, DPP4 inhibitors, SGLT2 inhibitors, GLP1 analogues etc.)	
*If a patient has already been taking one of these medications **on a stable dose for at least 12 weeks before baseline** (visit 2), he can be enrolled in the study and continue to take them during the study, except for the glucose-lowering agents insulin, sulfonylurea agents/analogues and thiazolidinediones/ glitazones, which are **not** allowed during the core study.*	
Dose adjustments or withdrawal of the following medications should be avoided during the core study:	
Cholesterol- or lipid lowering agents (e.g. HMG-CoA-inhibitors/statins, fibrates, nicotinic acid, ezetimibe, colestyramin, colestipol)	

Prohibited treatments during extension period

There are **no treatment restrictions** during the extension period, any treatments can be used.

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

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

[c] Oral, i.v., i.m., s.c.,. Exceptions: Inhalative corticosteroids (CS) with only a topical effect (e.g., to treat asthma) are not considered "**systemic** immunomodulating treatments" and are therefore acceptable as co-medication. The use of intra-articular and peri-articular corticosteroids is permitted throughout the study for treatment of symptoms of psoriatic arthritis that cannot be sufficiently controlled by study treatment and/or concomitant non-steroidal anti-inflammatory drugs (NSAIDS).

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

[e] **Mild to moderate topical corticosteroids are allowed only during the screening period if used only on the face, scalp and/or anogenital area. The use must be stopped 12 hours prior to first study medication administration. Urea (up to 5%) is allowed throughout the complete study, but must also be stopped 12 hours prior to each study visit.**

[f] **Urgent medical cases are excluded from this regulation**. These cases have to be documented in the eCRF.

*** Inactivated virus vaccinations are allowed

[g] If study treatment for psoriasis (i.e. secukinumab) is discontinued during the core study, then all restrictions for prohibited psoriasis treatments are lifted and the patient may be treated with concomitant topical, conventional systemic and/or biologic psoriasis treatments and/or phototherapy.

[h] If the lifestyle intervention is discontinued during the core study, then all restrictions for prohibited treatments for metabolic syndrome are lifted and the patient may be start other concomitant treatments for metabolic syndrome and/or change the dosage of treatments for metabolic syndrome that are already being administered.

5.5.9 Emergency breaking of assigned treatment code

Not applicable as the study has an open-label design.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the core study when the patient has completed the last visit planned of the core study. During the following extension period lifestyle intervention is offered to all patients. Patients from arm B can continue their already ongoing lifestyle intervention, patients from arm A can start a lifestyle intervention. In case a patient from arm B does not want to continue his lifestyle intervention during the extension period or a patient from arm A does not want to start a lifestyle intervention, he still has to participate in the extension period, which means he has to show up for dermatological study visits during the extension period.

During the extension phase no study drug will be supplied by Novartis. Investigators or treating physicians are free to choose suitable therapies for continued psoriasis treatment.

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

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment (Secukinumab or lifestyle intervention or both) is stopped earlier than the protocol planned duration and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment (Secukinumab or lifestyle intervention or both) for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.6 and Section 7.6)
- Use of prohibited treatment as per recommendations in Table 5-1
- Any situation in which study participation might result in a safety risk to the patient
- Emergence of the following adverse events: AEs that in the judgment of the investigator/qualified site staff, taking into account the subject's overall status prevent the subject from continuing study treatment

- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study
- Severe infections

If discontinuation of study treatment occurs during the core study, the patient should NOT be considered withdrawn from the study.

After study treatment discontinuation (i.e. discontinuation of secukinumab, lifestyle intervention or both) the patient will continue to attend regular study visits as per visit schedule and all assessments will be performed as planned. If one study treatment is discontinued (i.e. secukinumab or lifestyle intervention) this should not lead to discontinuation of the other, unless there is a reason for discontinuation of the other (see above for a list of reasons for discontinuation).

If a study treatment is discontinued, adequate replacement for this treatment may be sought outside of the study despite continued study participation:

- If secukinumab is discontinued, adequate concomitant drug treatment for psoriasis may be administered outside of the study. This does not require withdrawal of the patient from the study. In this case, there are no restrictions for concomitant psoriasis treatments (including topical, conventional systemic and biological drug treatments and phototherapy), even if the patient is still participating in the core or extension study period.
- If lifestyle intervention is discontinued, adequate concomitant treatment for metabolic syndrome may be administered outside of the study. This does not require withdrawal of the patient from the study. In this case, there are no restrictions for concomitant treatments of metabolic syndrome (including but not limited to drug treatments or other lifestyle interventions, dose adjustments and/or new treatments are permitted), even if the patient is still participating in the core or extension study period.

The reason for study treatment discontinuation should be recorded in the eCRF.

5.6.3 Withdrawal of informed consent

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

- Does not want to participate in the study anymore/ Does not want to participate in the lifestyle intervention any more

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

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

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

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

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

5.6.4 Loss to follow-up

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

5.6.5 Early study termination by the sponsor

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

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Patients should be seen for all study visits on the designated day, or as close to it as possible. Recommended study visit windows are +/- 2 days for visits 2 – 6, +/- 5 days for visits 7 – 12 and +/- 7 days for visits E1 – E3. The same visit windows are recommended for the lifestyle intervention visits associated to the study visits.

Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. In case of premature discontinuation during the core study the final visit is the week 28 visit, in the case of premature discontinuation during the extension period the final visit is the week 56 visit. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Table 6-1 lists assessments that are recorded in the clinical database (marked "X" if entered via the eCRF or "C" if entered centrally, e.g. via a central laboratory) and assessments that are source documentation only (marked "S"). Assessments that are source documentation only will not be entered into the eCRF.

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

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

Table 6-1 Assessment schedule

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	E1	E2	E3	US V[4]
Week	-4 - -1	0	1	2	3	4	8	12	16	20	24	28	36	44	56	
Day	-28 - -7	1	8	15	22	29	57	85	113	141	169	197	253	309	393	
Obtain informed consent	X															
Obtain informed consent for biomarker substudy[9]	X															
Demographics	X															
Inclusion/exclusion criteria[1]	X	X														
Smoking history	X											X			X	
Medical history and prior medications	X															
Cardiovascular/ metabolic medical history	X															
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	S	S							S			S			S	S[5]
Height	X															
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Waist and hip circumference	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Routine Laboratory‡	C	C		C		C	C	C	C	C	C	C	C	C	C	C[5]
Fasting Laboratory[6]	C	C					C		C			C	C	C	C	C[5]
QuantiFERON test[2]	C															C[5]
Serum pregnancy test[3]	C											C			C	C[5]
Local pregnancy test		X														C[5]
Urine dipstick	X	X							X			X				X[5]
PASI / BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
DLQI©	X	X				X	X	X	X	X	X	X	X	X	X	
WHO-5		X				X	X	X	X	X	X	X	X	X	X	
Self-assessed itch, pain, scaling		X				X	X	X	X	X	X	X	X	X	X	
Biomarker sub-study (**fasting**)[9]		X							X			X				
(S)AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X														
Study treatment or dispensing		X	X	X	X	X	X	X	X	X	X					
Drug accounting		X	X	X	X	X	X	X	X	X	X	X				X[5]
Lifestyle Intervention visit[8]		X	X	X	X	X	X		X		X		X	X	X	

X = assessment to be recorded on clinical database; S = assessment to be recorded on source documentation; C = centrally analyzed laboratory or questionnaire results
‡: Hematology (incl differential blood analysis) and clinical chemistry
[1]These assessments are supported by and stored within the source documentation Data relating to inclusion/exclusion criteria are captured in the corresponding CRF
[2]A repeat QuantiFERON® TB-Gold In-Tube test is recommended if the result of the first QuantiFERON® TB-Gold In-Tube test is "indeterminate" The subject must be referred for a follow-up tuberculosis workup (as per local guidelines) if either the first or the repeat test is "positive" or if the results of both tests are "indeterminate" If the first test is indeterminate, the investigator may decide not to repeat the test and to proceed directly to the workup, though this is not recommended The subject will not be eligible for randomization if "active tuberculosis is present "or if "latent tuberculosis is present" and is untreated as per local guidelines
[3]Only for females of child-bearing potential
[4]Unscheduled visits might be required e g if patients observe symptoms between scheduled visits or for safety reasons The safety assessments listed herein may be performed at the discretion of the investigator as needed to resolve the reason for the unscheduled visit (S)AE assessment and concomitant medications are mandatory for all unscheduled visits

[5] Only if necessary according to the treating physician
[6] Patients must show up in fasting (8 hours) state
[redacted]
[8] For patients in arm B
[9] Only for participating patients

6.1 Information to be collected on screening failures

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

6.2 Patient demographics/other baseline characteristics

6.2.1 Demographics

Subject demographic data will include: year of birth, gender, race, and child-bearing potential as well as postmenopausal status (for females only).

6.2.2 Psoriasis medical history/previous psoriasis therapies

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

- The date of first symptoms of plaque-type psoriasis
- The date of first diagnosis of plaque-type psoriasis
- The previous treatments of psoriasis (including phototherapy and/or photochemotherapy) and the reason for discontinuation. If a Novartis drug (e.g. Sandimmun/ cyclosporine A) was discontinued due to an adverse event, abuse/ misuse or pregnancy a spontaneous report needs to be sent to the local Novartis Patient Safety department. Topical therapies are only collected for the last 24 month prior to signing the informed consent.
- The presence of psoriatic arthritis and date of first diagnosis

6.2.3 Smoking history

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

6.2.4 Relevant medical history/current medical conditions

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

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

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

6.2.5 Prior and concomitant medications

Prior medications taken over the 6 months preceding study enrollment will be captured at the screening visit. Medication taken parallel to the study treatment will be captured as concomitant medication on all following visits.

6.2.6 Cardiovascular and metabolic medical history

Relevant cardiovascular and metabolic medical history (e.g. diabetes, hypertension, hypercholesterinemia) will be assessed in the cardiovascular and metabolic medical history eCRF.

6.2.7 Determination of the tuberculosis status

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

QuantiFERON TB-Gold In-Tube assay

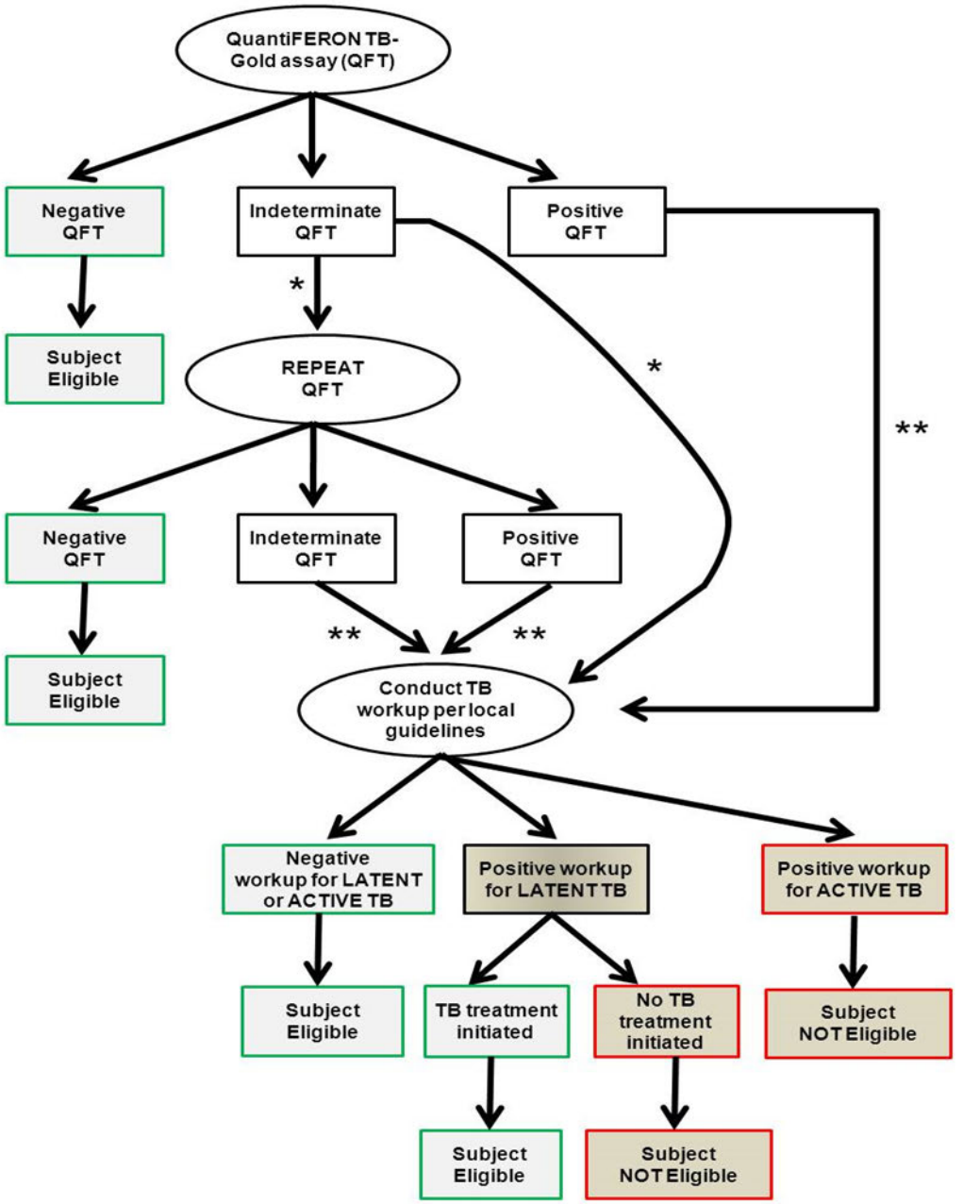
A QuantiFERON® TB-Gold In-Tube assay (QFT) to screen a population for latent tuberculosis infection (Doherty et al., 2008) will be used at Screening to evaluate the subjects' eligibility for the study. This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous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

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

- If the test result is **negative**, the subject may be randomized.
- If the test result is **positive**, the investigator should perform a work-up for the test result as per local procedures. If a TB work-up was conducted prior to the screening of the subject, results of the work-up can be used to assess eligibility if the work-up was conducted within 12 weeks prior to randomization.
    - Subjects **positive** for latent TB per work-up may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration. Subjects positive for active TB per work-up are not eligible for the study. Subjects negative for TB (no signs of latent or active TB) per work-up may be randomized to the trial.

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

Figure 6-1 Tuberculosis screening flowchart



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

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

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

6.3 Treatment exposure and compliance

All doses of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page (visit specific and summary pages). Compliance to the planned site administration schedule is expected to be high since the study treatment will be administered by the investigator or in the presence of the investigator or study personnel at pre-defined visits (except 1 allowed home administration in selected cases at the discretion of the investigator). Compliance will also be assessed and confirmed by a field monitor by drug accountability logs, by documentation and by the qualified site personnel that is responsible for treatment dispensation, preparation, administration and accountability.

The same applies for the lifestyle intervention, participation in all lifestyle intervention counseling visits will be recorded in the eCRF.

6.4 Efficacy

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

All other remaining study visit procedures (e.g. laboratory sample collection, vital signs, waist/ hip circumference measurement, questionnaires etc.) must also be completed prior to administration of study treatment.

6.4.1 PASI/ BSA

Assessment of total body surface area (BSA) and Psoriasis Area and Severity Index (PASI)

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 four percentages will be added up to estimate the total BSA affected by plaque-type psoriasis.

The PASI scoring system is further described in Table 6-3.

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

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

The keys for the letters are provided in Table 6-2.

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

The baseline value for analysis of the PASI is collected at the Randomization Visit.

If results of BSA and PASI assessment fulfill criteria for an (serious) adverse event, the investigator has to document it accordingly.

Table 6-2 The PASI scoring system

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

Definitions of efficacy variables based on PASI

The following definitions will be used in this study based on the CHMP guidelines for psoriasis (CHMP/EWP/2454/02 2004):

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

6.4.2 Biomarkers of glucose and lipid metabolism

Biomarkers of glucose metabolism: HbA1c, fructosamine and fasting plasma glucose.

Biomarkers of lipid metabolism: Total cholesterol, triglycerides, LDL, HDL.

These markers will be assessed as part of the routine or fasting laboratory, time points are shown in table 6-1.

6.4.3 Biomarkers of systemic inflammation

Biomarker of systemic inflammation: hsCRP

This marker will be assessed as part of the routine laboratory, time points are shown in table 6-1.

6.4.4 Weight and height

Height and body weight will be measured as listed in table 6-1, height in centimeters (cm) and body weight in kilogram (kg) (to the nearest 0,1 kg).

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

6.4.5 Waist and hip circumference

Waist and hip circumference will be measured as listed in table 6-1, both in centimeters (cm). **Waist circumference measurement is taken with a tape measure at the approximate midpoint between the inferior margin of the last palpable rib and the top of the iliac crest (as suggested by WHO and IDF).** The accuracy of waist and hip circumference measurements depends on corrects tightness and positioning of the measuring tape: Measurements should be made with a **stretch-resistant tape**, which should be snug around the body **parallel to the floor/ in a horizontal plane**. The tape should **not** be pulled so that tight that it is constricting. A standardized tape supplied by Novartis has to be used.

6.4.6 Blood pressure and pulse

Resting blood pressure will be assessed at every scheduled visit as indicated in Table 6-1 according to the 2013 European Society for Cardiology guidelines for the management of arterial hypertension (Mancia et al., 2013). Whenever possible, assessments should be performed by the same study site staff member throughout the study. **It is crucial that blood pressure is measured in the resting state and therefor appropriate resting conditions are ensured**:

Coffee, black tea, caffeine and smoking must be avoided before the measurement is performed. **After the subject has been sitting and resting in a quiet environment for five minutes**, with back supported and both feet placed on the floor, systolic and diastolic **blood pressure will be measured twice (measurements separated by 2 minutes)** using an **automated, validated device**, with an appropriately sized cuff. A standard bladder (12-13 cm wide and 35 cm long) should be used, but a larger and a smaller bladder have should be available for large (arm circumference >32 cm) and thin arms. The cuff should be at the heart level of the patient. Measurements will be recorded in the source documentation and **the average of the two**

measurements will be entered on the Vital Signs eCRF. The same applies for the pulse measurement.

6.4.7 Appropriateness of efficacy assessments

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

Biomarkers of glucose: HbA1c and fasting plasma glucose are standard parameters used in daily clinical practice to monitor glucose metabolism and recommended in German national guidelines for diagnosis of diabetes (Kerner et al., 2014). Fructosamine is not as widely used as HbA1c or fasting plasma glucose but offers the advantage of indicating the quality of glucose control during the last 2-3 weeks in contrast to HbA1c, which is an indicator of glucose control during the last 8-12 weeks (Ribeirio et al., 2016).

Biomarkers of lipid metabolism: total cholesterol, triglycerides, HDL and LDL are standard parameters used in daily clinical practice to monitor lipid status and assess cardiovascular risk profile. They are recommended in European guidelines for diagnosis and management of dyslipidemias (Reiner et al., 2011).

CRP is the most widely used blood marker of systemic inflammation. The detection method used for the hsCRP test allows more sensitive testing and was used in several psoriasis clinical trials as a marker of systemic inflammation (Puig et al., 2014; Gkalpakiotis et al., 2016).

Weight, BMI and hip circumference are clinical routine parameters for the assessment of obesity. Measurement of systolic and diastolic blood pressure is clinical routine for the assessment of hypertension.

6.5 Safety

Blood withdrawals and safety assessments should be done prior to study treatment administration. Appropriate safety assessments (e.g. evaluation of AEs and SAEs including injection site reactions) should be repeated after the dose is administered. Several of the safety parameters are used as efficacy parameters as well and are therefore already described in the section 6.4 above (e.g hsCRP, blood pressure, body weight).

6.5.1 Physical examination

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

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

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

6.5.2 Vital signs

Vital signs (blood pressure and pulse measurements) will be assessed at every scheduled visit as indicated in Table 6-1. Whenever possible, assessments should be performed by the same study site staff member throughout the study. Please see detailed description of blood pressure measurement in section 6.4.6.

6.5.3 Height and weight

Height and body weight will be measured as listed in Table 6-1, height in centimeters (cm) and body weight in kilogram (kg) (to the nearest 0,1 kg).

Measurement is described in detail in section 6.4.4.

6.5.4 Laboratory evaluations

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

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

6.5.4.1 Routine laboratory

Routine laboratory measurements include clinical chemistry and hematology. They will be measured at all time points specified in Table 6-1.

Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count.

Clinical chemistry/ proteins: Urea, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, creatinine, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, uric acid, amylase, lipase, hsCRP, HbA1c (only at visits 1, 2, 7, 9, 11, 12, E1, E2, E3 included), fructosamine (only at visits 1, 2, 6, 7, 8, 9, 10, 11, 12, E1, E2, E3 included).

6.5.4.2 Fasting laboratory

Fasting laboratory measurements will be made at all time points specified in Table 6-1. **Fasting for 8 hours duration with water ad libitum is required prior to blood draws**. Subjects should avoid smoking within in the hours preceding the blood draws.

Fasting laboratory: Total cholesterol, triglycerides, HDL, LDL, fasting plasma glucose.

6.5.4.3 Urinalysis

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

6.5.5 Electrocardiogram (ECG)

Not applicable in this study.

6.5.6 Pregnancy and assessments of fertility

In all women who are not sterilized or are of childbearing potential a serum pregnancy test (ß-hCG) must be performed as indicated in Table 6-1.

Any woman with a confirmed positive pregnancy test during Screening is not eligible for randomization. A positive serum pregnancy test during the treatment phases of the study requires immediate interruption of study treatment.

6.5.7 Appropriateness of safety measurements

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

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

6.6 Other assessments

6.6.1 Clinical Outcome Assessments (COAs)

6.6.1.1 Clinician Reported Outcomes (ClinRO)

Not applicable.

6.6.1.2 Patient Reported Outcomes (PRO)

Patient reported outcomes will be assessed by the following validated instruments, each of which will be performed as indicated in Table 6-1:

- Dermatology Life Quality Index (DLQI©)
- Self-assessed pain, itching, scaling
- WHO-5

All these quality of life assessments should be completed by the subject before they see the study physician (investigator or designee) who will perform the investigator assessments.

All these quality of life assessments will be completed **in German language**. The subject should be given sufficient space and time to complete the questionnaires. The study coordinator should check the questionnaires for completeness and encourage the subject to complete any missing responses. Prior to clinical examination, the investigator should review the completed

questionnaires for responses that may indicate potential AEs or SAEs. If AEs or SAEs are confirmed, the investigator must record the events as per instructions given in Section 7 of the protocol.

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

Dermatology Life Quality Index (DLQI©)

The DLQI© is a 10-item general dermatology disability index designed to assess Health-related quality of life (HRQoL) in adult subjects 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 four response categories ranging from 0 (not at all) to 3 (very much). "Not relevant" is also a valid response and is scored as 0. The DLQI© total score is a sum of the 10 questions. Scores range from 0 to 30, with higher scores indicating greater HRQoL impairment. Each subscale of the DLQI© may also be analyzed separately.

Subject's self-assessed pain, itching and scaling

A self-administered, 11-point numeric rating scale (NRS, 0-10) will be used to evaluate the subject'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

Subjects have to rate their pain, itching, and scaling from 0 to 10 (11-point scale), with the understanding that the 0 represents the absence or null end of the pain, itching, or scale intensity (i.e., no pain, itching or scaling) and the 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.

WHO-5

The 5-tem World Health Organization Well-Being Index (WHO-5) is a validated, short questionnaire consisting of 5 simple questions, assessing subjective psychological well-being of the respondents. It is among the most widely used questionnaires for the assessment of psychological well-being and has been successfully applied across a wide range of study fields.

The measure is self-administered and takes approximately one minute to complete. The recall period is the previous two weeks. Each item has 6 response categories, ranging from 5 ("the whole time") to 0 ("at no time point"). The WHO-5 total score is the sum of the 5 questions. Each subscale of the WHO-5 may also be analyzed separately.

6.6.1.3 Performance Outcomes (PerfO)

Not applicable.

6.6.1.4 Observer Reported Outcomes (ObsRO)

Not applicable

6.6.1.5 Proxy Reported Outcomes

Not applicable.

6.6.2 Resource utilization

Not applicable.

6.6.3 Pharmacokinetics

Not applicable.

6.6.4 DNA sampling

Not applicable.

Pharmacogenetics

Not applicable.

6.6.5 Biomarker substudy

A biomarker sub-study will be performed during the core study to explore the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on biomarkers including but not limited to those linked to lipid, glucose, muscle and bone metabolism, liver fibrosis/steatosis, heart failure, as well as to inflammatory processes in a subgroup of 100 patients (50 treated with secukinumab and lifestyle intervention and 50 treated with Secukinumab alone). At baseline (week 0), week 16 and week 28 the following markers will be assessed using fasting blood samples: Free fatty acid serum profile, sThy-1, adiponectin, leptin, insulin, HOMA-IR, proinsulin, IL-6, TNF-alpha, M30 assay, IL-1 beta, IL-1Ra, IL-18, IL-18bp, P1NP, CTX, RANKL, OPG, sclerostin, NT-proBNP, CD154, and a 30-panel multiplex inflammatory cytokine and chemokines panel.

The markers will be assessed centrally.

7 Safety monitoring

7.1 Adverse events

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

present before first intake of study drug are only considered adverse events if the worsen after study start.

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

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1. Clinically significant abnormal laboratory values will also be assessed for the following parameters of the biomarker sub-study (only for patients participating in the biomarker sub-study): Adiponectin, leptin, insulin, HOMA-IR, proinsulin, IL-6, TNF-alpha, M30 assay, NT-proBNP.

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

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment and/or to the lifestyle intervention
  - "No Relationship to study treatment and lifestyle intervention" or
  - "Relationship to study treatment" or
  - "Relationship to lifestyle intervention" or
  - "Relationship to both study treatment and lifestyle intervention or indistinguishable"
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding study drug or lifestyle intervention
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

All adverse events must be treated appropriately. The action taken to treat the adverse event should be recorded on the Adverse Event eCRF. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- study treatment dosage increased/reduced
- lifestyle intervention intensity increased/reduced
- study treatment and/or lifestyle intervention interrupted/withdrawn
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)

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

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

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

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)

  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

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

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

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

7.2.2 SAE reporting

To ensure patient safety, every SAE must be reported to Novartis safety within 24 hours of learning of its occurrence.

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

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

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has

resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

SAE reporting in the Extension Period:

In the Extension Period, the treating physician is free to choose suitable psoriasis therapy for each patient.

Therapy with marketed Secukinumab or another Novartis product:

Any SAE occurring in the Extension Period should be notified to Novartis Patient Safety within 24 hours of learning of its occurrence, .regardless of causality assessment. Furthermore, any SAE occurring until 10 weeks (70 days) after the last study visit, or 12 Weeks (84 days) following the last administration of marketed Secukinumab, or 30 days after the subject has stopped study participation (whichever is later) must be reported to Novartis.

Also any non-serious adverse event needs to be documented in the Adverse Events CRF section during study participation.

Therapy with non-Novartis products:

Any SAE occurring in the Extension Period under therapy with a non-Novartis product is sent to Novartis Patient Safety regardless of causality, **within 12 weeks** after last administration of investigational drug Secukinumab or marketed Secukinumab (if switch is performed during the Extension Period). During the 12 weeks period, physician should clearly state on the SAE form which treatment (current non-Novartis therapy or previous Secukinumab treatment) has been assessed as suspected or not. After this 12 weeks period, only SAE need to be forwarded to Novartis for which causality was assessed as suspected for Secukinumab by investigator. Furthermore, any suspected SAE under a non-Novartis drug should be forwarded to the respective manufacturer or the regulatory authority by the investigator.

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

7.3 Liver safety monitoring

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

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

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

Every liver laboratory trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 14-2 in Appendix 2.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

7.5 Pregnancy reporting

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

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

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

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may

analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to US CFR 21Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

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

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

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

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. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

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

9.1 Analysis sets

The following analysis sets will be used in this study:

The **Enrolled Set** will include all patients who provided informed consent.

The **Randomized Set** will consist of all patients who were randomized into this study at Baseline.

The **Safety Set (SAF)** will consist of all patients who received at least 1 dose of study treatment.

The **Full Analysis Set (FAS)** will consist of all patients who were randomized into this study at Baseline and received at least one dose of study treatment. Data will be analyzed according to the treatment assigned at randomization.

9.2 Patient demographics and other baseline characteristics

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

9.3 Treatments

9.3.1 Study treatment

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

The duration of exposure to study treatment will be summarized by treatment group. In addition, the number of patients with exposure of certain thresholds of study treatment will be displayed. Compliance will be calculated based on documented study drug administrations, syringe counts and documented participation in lifestyle intervention and displayed by treatment group.

9.3.2 Prior and concomitant treatment

Prior and concomitant treatments and non-drug therapies will be summarized by treatment group in separate tables.

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

Treatments will be presented in alphabetical order, by anatomical therapeutic classification (ATC) codes and grouped by anatomical main group. The overall number and percentage of patients receiving at least 1 treatment in a particular ATC will also be presented in summary tables.

9.4 Analysis of the primary variable(s)

9.4.1 Primary Variable(s)

The primary variable is the percentage of patients achieving PASI90 at week 28 in both randomized treatment arms, Secukinumab alone and Secukinumab combined with lifestyle intervention.

9.4.2 Statistical model, hypothesis, and method of analysis

The null hypothesis to be rejected is that the odds of response Week 28 are equal in both treatment groups. The corresponding alternative hypothesis is that the odds of response at Week 28 are higher under Secukinumab combined with lifestyle intervention compared to Secukinumab alone.

Let pj denote the proportion of responders at Week 28 for treatment group j, j=0, 1, where

- 0 corresponds to Secukinumab combined with lifestyle intervention
- 1 corresponds to Secukinumab alone

The following hypotheses will be tested:

H0: (p1 / (1- p1)) / (p0 / (1- p0)) = 1 versus HA: (p1 / (1- p1)) / (p0 / (1- p0)) $\neq$ 1

In other words:

HA: The odds ratio of achieving a response at Week 28 for Secukinumab combined with lifestyle intervention vs Secukinumab alone is different from 1.

The primary analysis will be performed comparing treatments with respect to the primary efficacy variable in a logistic regression model with the factors treatment, center and covariate baseline PASI. The odds ratio and its 95% confidence interval (CI) and p-value will be given. The null hypothesis of equal odds will be rejected if the 2-sided p-value from the logistic regression model for the factor “treatment” is < 0.05; however, superiority of Secukinumab combined with lifestyle intervention will be claimed only if the direction is correct, i.e. if the odds of response are larger under Secukinumab combined with lifestyle intervention.

9.4.3 Handling of missing values/censoring/discontinuations

Patients who do not have a valid PASI assessment at week 28 will be regarded as non-responders for the primary analysis. Non-responder imputation will also be applied to all secondary response variables. For continuous secondary endpoints, all available measurements will be included in the MMRM.

9.4.4 Sensitivity analyses

The primary endpoint will be analyzed by means of a Cochran-Mantel-Haenszel (CMH) test. This test will be stratified by center. Treatment groups will be compared with respect to the proportion of responders using the Cochran-Mantel-Haenszel test statistics. The corresponding p-values will be based on the CMH statistics which follows a Chi-square distribution with one degree of freedom.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

PASI 75, 90 and 100 at weeks 1, 2, 3, 4, 8, 12, 16, 20, 24 and 28 will be analyzed analogous to the primary endpoint. Absolute PASI scores will be analyzed using a Mixed Model for Repeated Measurements (MMRM) with factors treatment, center, visit, visit*treatment interaction and covariate baseline PASI. The raw- as well as the adjusted (LS-) means and their differences between treatment groups will be calculated for each visit together with their corresponding 95% confidence intervals and p-values.

The same MMRM model will also be used for the analyses of the other continuous secondary endpoints hsCRP, HbA1c, fructosamine, fasting plasma glucose, LDL, HDL, cholesterol, triglycerides, waist circumference, body weight, BMI, systolic and diastolic blood pressure, absolute DLQI, relative change of DLQI, proportion of patients with DLQI 0/1, absolute WHO-5, relative change in WHO-5, absolute self-assessed itch, pain, scaling, relative change in self-assessed itch, pain, scaling in both treatment arms throughout the duration of the core study, and activity levels.

9.5.2 Safety variables

9.5.2.1 Adverse events

Treatment emergent adverse events (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity) will be summarized by preferred term up to 12 weeks (84 days) after the last dose. Non-treatment-emergent AEs will be listed in a listing but not summarized.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a patient reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a patient reported more than one adverse event within the same primary system organ class, the

patient will be counted only once with the greatest severity at the system organ class level, where applicable. Furthermore, a listing of all adverse events, including SAE, will be provided.

Serious adverse events will also be summarized.

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

9.5.2.2 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, clinical chemistry and urinalysis). Descriptive summary statistics for the change from Baseline to each study visit will be presented.

These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from Baseline will only be summarized for patients with both Baseline and Post-Baseline assessments.

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

9.5.2.3 Vital signs

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

9.5.3 Resource utilization

Not applicable.

9.5.4 Pharmacokinetics

Not applicable.

9.5.5 DNA

Not applicable.

9.5.6 Biomarkers

See section 9.6

9.5.7 PK/PD

Not applicable.

[redacted]

[redacted]

9.7 Time points of analysis

A first analysis of the core study (primary, secondary [redacted] related to the core study) will be performed after all subjects have completed the core study. [redacted]

The two analyses will be reported in separate clinical study reports.

9.8 Sample size calculation

This study is primarily designed to demonstrate superiority of Secukinumab combined with lifestyle intervention vs Secukinumab alone in terms of PASI90 response at week 28. A PASI90 response of 81% at week 28 under Secukinumab alone in patients with metabolic syndrome is assumed. This number is based on a retrospective analysis performed with data from the CLEAR study, taking into account the slightly higher BMI of the patient population with metabolic syndrome (BMI 23-42 kg/m2, Albareda M et al., 2014) and the open-label design.

Evidence on effect size of lifestyle intervention on PASI response is relatively rare and assumptions were based on the following studies: A clinical study by Al-Mutairi et al. showed an absolute increase of 27% in PASI75 response to biologic treatment (Infliximab, Etanercept, Ustekinumab, Adalimumab) in overweight or obese, moderate to severe psoriasis patients undergoing weight reduction compared to patients not undergoing weight reduction (Al-Mutairi N et al., 2014) However the dietary regimen used in this study was highly restrictive and consecutively led to a strong mean weight loss (-13 kg vs + 1,5 kg in the control group after 24 weeks). Naldi et al. showed an absolute increase of 6% in PASI75 response to systemic treatment in overweight to obese, moderate to severe psoriasis patients undergoing diet and physical exercise compared to control patients. The lifestyle intervention in this study was less intensive and consecutively led to a smaller mean weight loss (-3kg vs -1.6 kg in the control group after 20 weeks). It seems that the extent of increase in PASI response correlates with the achieved weight loss, at least to a certain extent. PASI90 data were not available for both cited studies. The lifestyle intervention conducted in the present study is less intensive than the one applied by Al-Mutairi et al. but more intensive compared to Naldi et al. A lifestyle intervention very similar to the one applied in our study was previously able to show a mean weight loss of -3.8 kg vs. -1.4 kg after 1 year (Kulzer B et al., 2014). Maximum weight loss can already be expected after 3-4 month. As part of the lifestyle intervention program tracking devices will be used in the present study to further support the lifestyle intervention.

Based on these considerations and the fact that we are looking at PASI90 response in the present study, we assume an absolute increase of 9% in PASI90 response in the Secukinumab combined with lifestyle intervention arm to 90% PASI90 responders compared to 81% PASI90 responders in the Secukinumab alone arm. An absolute increase of 9% in PASI90 responders would also be clinically meaningful.

Based on these assumptions 342 patients per arm would provide a power of 90 % at a two-sided alpha of 0.05 to demonstrate that the percentage of PASI90 responders at week 28 is higher in

the Secukinumab combined with lifestyle intervention arm compared to the Secukinumab alone arm. In case the true effect size would only be 7.5 %, this sample size would still provide a power of 75 %. To compensate for some expected drop out and/or premature discontinuations, 380 patients per arm are planned to be recruited for this trial.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

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

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

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

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

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

11 Protocol adherence

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

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

11.1 Protocol amendments

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

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13 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests. Notable values for blood pressure and pulse are presented in section **Error! Reference source not found.**.

No specific action is pre-defined within this protocol to respond to specific abnormal laboratory values except for the follow up requirement for liver events as specified in Appendix 2, as it will be decided by the investigator/qualified 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 subject.

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

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

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

Table 14.1 Liver Event Definitions

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

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

Table 14-2 Liver Event Follow Up Requirements

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

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

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

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

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