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AIN457/secukinumab

Clinical Trial Protocol CAIN457ADE15 / NCT04237116

A randomized, double-blind, multicenter, 24-week study of subcutaneous secukinumab to assess anti-interleukin-17A treatment in plaque psoriasis patients with coexisting non-alcoholic fatty liver disease (pINPOINt)

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List of abbreviations

AE	Adverse Event
AIDS	Autoimmune Deficiency Syndrome
[redacted]	[redacted]
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUDIT	Alcohol Use Disorders Identification Test
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
[redacted]	[redacted]
CFR	US Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
DBP	Diastolic Blood Pressure
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
[redacted]	[redacted]
EMA	European Medicines Agency
[redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
[redacted]	[redacted]
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
[redacted]	[redacted]
[redacted]	[redacted]
Hb	Hemoglobin
HbA1c	Glycated Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
hCG	Human Chorionic Gonadotropin
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFG	Increased Fasting Glucose
[redacted]	[redacted]
IL	Interleukin
INR	International Normalized Ratio
IQR	Interquartile range
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDL	Low Density Lipoprotein
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NAFL	Non-Alcoholic Fatty Liver
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
NYHA	New York Heart Association
OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PCR	Protein-Creatinine Ratio
PFS	Prefilled Syringe
[redacted]	[redacted]
PRO	Patient Reported Outcomes
PT	Preferred Term
QMS	Quality Management System
RAS	Randomized Analysis Set
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAF	Safety Set
SBP	Systolic Blood Pressure
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type-2 Diabetes Mellitus
TB	Tuberculosis
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
[redacted]	[redacted]
TNFα	Tumor Necrosis Factor Alpha

Tregs	T Regulatory
UDCA	Ursodeoxycholic Acid
ULN	Upper Limit Normal
[redacted]	[redacted]
WBC	White Blood Cells
WHO	World Health Organization
WoC	Withdrawal of Study Consent

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Biologic samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study patient.
Cohort	A specific group of patients fulfilling certain criteria and generally treated at the same time.
Control drug	A study drug (active or placebo) 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
Electronic data capture	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
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last patient or at a later point in time as defined by the protocol
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized patients	Mis-randomized patients are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned

Randomization number	A unique identifier assigned to each randomized patient
Screen failure	A patient who did not meet one or more criteria that were required for participation in the study
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
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first patient.
Study treatment	Any single drug or combination of drugs or intervention administered to the patient as part of the required study procedures
Study treatment discontinuation	When the patient permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 1

Amendment rationale

The main purpose of this amendment is to allow for participation of study sites in Spain and to correct inconsistencies. Additionally, an exclusion criterion was modified to exclude latent tuberculosis patients without completed tuberculosis treatment prior to screening as this treatment may affect liver function parameters that are relevant to secondary endpoints.

Changes to the protocol

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

A selection of the main changes encompasses:

[redacted]

- Section 5.2 – Exclusion criteria:
  - Exclusion criterion 10 was modified in order to exclude patients with a positive QuantiFERON-TB-Gold Plus test in whom the presence of latent tuberculosis was established and tuberculosis treatment was not completed prior to screening. In addition, it was specified that during latent tuberculosis treatment, had to remain below 2x compared to pre-treatment ALT value.
  - Exclusion criterion 13: Definition of uncontrolled diabetes was clarified (applicable for Type II diabetes only).
  - Exclusion criterion 14 ("platelets < 100.000 /µL") was removed as this information is already included in the definition in Exclusion criterion 15.
- Section 6 – Treatment:
  - In Table 6-1 (Section 6.1.1), the information on the sponsor was corrected to „Sponsor (local)".
  - Country-specific procedures for Spain e.g. for the handling of study treatment, were added to the following sections and information regarding the processes in Germany was added, if relevant:
    - Section 6.3.1 – Patient numbering
    - Section 6.3.2 – Treatment assignment, randomization
    - Section 6.6.2 – Emergency breaking of assigned treatment code
    - Section 6.7 – Preparation and dispensation
    - Section 7 – Informed consent procedures
- Section 8 – Visit schedule and assessment: Changes have been made to Table 8-1: it was clarified that INR is assessed only at screening visit.
- Section 8.2.2 – Tuberculosis screening: This section was updated to reflect the changes of exclusion criterion 10.

[redacted]

- Section 8.4 – Laboratory evaluations: Removal of parameters that will no longer be assessed during the study from table 8-4.
- Section 8.5.1 – Alcohol use disorder identification test (AUDIT): Instead of the patients completing the questionnaire on their own, the site staff will perform the AUDIT together with the patient in the form of an interview. Consequently, AUDIT was removed from section 8.5.2 – Patient reported outcomes.

Additionally, this protocol amendment includes changes to increase clarity and consistency of the text. Consequently, changes were incorporated directly into the protocol with track changes, even if not listed specifically in this section.

The changes herein do not affect the Informed Consent. None of the changes described in this amended protocol are made due to newly emerged safety considerations.

Protocol summary

Protocol number	CAIN457ADE15
Full title	A randomized, double-blind, multicenter, 24-week study of subcutaneous secukinumab to assess anti-Interleukin-17A treatment in Plaque Psoriasis patients with coexisting NAFLD (pINPOINt)
Brief title	A study of secukinumab treatment in patients with plaque psoriasis and coexisting non-alcoholic fatty liver disease (NAFLD)
Sponsor and clinical phase	Novartis, Phase 3b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The aim of this study is to assess the therapeutic efficacy of secukinumab on the psoriatic skin and to explore the anti-inflammatory (reduction of hepatic inflammation and cell damage), anti-steatotic (reduction of hepatic triglyceride content) and anti-fibrotic (reduction of hepatic fibrosis) effects of secukinumab in patients with psoriasis and coexisting NAFLD.
Primary objective	To demonstrate superiority of secukinumab compared to placebo in patients with moderate to severe chronic plaque-type psoriasis and NAFLD with respect to psoriasis area and severity index (PASI)90 response at Week 12.
Secondary objectives	• To evaluate the effect of secukinumab compared to placebo on hepatic inflammation in patients with moderate to severe psoriasis and NAFLD with respect to serum alanine aminotransferase (ALT) levels at Week 12. • To evaluate the effect of secukinumab in patients with moderate to severe psoriasis and NAFLD compared to placebo on quality of life with respect to dermatology life quality index (DLQI) at Week 12.
[redacted]	

Study design	This is a randomized, placebo-controlled, double-blind, parallel-group, interventional, multicenter study in patients with moderate to severe plaque psoriasis and coexisting NAFLD. This study consists of a Screening Period (up to 4 weeks) and 2 Treatment Periods (covering 24 weeks in total). **Treatment period 1** Patients will be randomized 2:1 to either receive secukinumab 300 mg s.c. (in 2 × 150 mg PFS) or placebo (2 × PFS) at Baseline, Week 1, Week 2, Week 3, Week 4 and Week 8. **Treatment period 2** Starting from Week 12, all patients will receive secukinumab 300 mg s.c. up to Week 20. Patients who were randomized to placebo during Treatment Period 1 will receive secukinumab 300 mg s.c. at Week 12, Week 13, Week 14, Week 15, Week 16, and Week 20. Patients who were randomized to secukinumab during Treatment Period 1 will receive secukinumab 300 mg s.c. at Week 12, Week 16, and Week 20, and placebo at Week 13, Week 14 and Week 15 to maintain the blind.
Population	Patients with moderate to severe plaque psoriasis and coexisting NAFLD who are candidates for systemic psoriasis therapy will be included in this study.
Inclusion criteria	1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study, and must provide written, signed and dated informed consent before any study assessment is performed . 2. Men and women ≥ 18 years of age at the time of consent. 3. Moderate to severe plaque-type psoriasis diagnosed for at least 6 months prior to Screening with a PASI of >10 at baseline. 4. Candidate for systemic therapy, defined as a subject having moderate to severe chronic plaque-type psoriasis that is inadequately controlled by: • Topical treatment and/or, • Phototherapy and/or, • Previous systemic therapy. 5. Diagnosis of NAFLD by either ultrasound at Screening or liver histology within 6 months before Baseline. 6. Obesity with BMI > 25 kg/m^2 at Screening. 7. Elevation of ALT 1.2 to 3.0 × ULN. 8. Liver fat ≥ 8% at Screening as determined by the reading of the central MRI vendor of locally produced images. Note: the MRI assessment should only be performed after eligibility has been confirmed for all other Screening assessments.

Exclusion criteria	1. Forms of psoriasis other than chronic plaque-type psoriasis at Screening. 2. Drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium) at Screening and baseline. 3. Ongoing use of prohibited treatments (see Section 6.2.2 of main protocol). Respective washout periods detailed in this section have to be adhered to. 4. History of hypersensitivity to any of the study drug constituents. 5. Pregnant or nursing (lactating) women. 6. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the study or longer if required by locally approved prescribing information (e.g., 20 weeks in the European Union). 7. Previous treatment with biological drug targeting IL-17 or the IL-17 receptor (including prior treatment with secukinumab, ixekizumab, or brodalumab). 8. Past medical history record of infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C prior to screening. 9. Active systemic infections during the last two weeks (exception: common cold) prior to randomization or any infection that reoccurs on a regular basis. 10. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuantiFERON-TB-Gold Plus (QFT) test at screening. Subjects with a positive or indeterminate QFT test may participate in the study if full tuberculosis work up (according to local practice/guidelines) was completed within 12 weeks prior to randomization and establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to local guidelines must have been completed prior to screening. During treatment of latent tuberculosis, ALT had to remain below 2x compared to pre-treatment ALT value. 11. Significant medical problems, including but not limited to: • Congestive heart failure [New York Heart Association status of class III or IV]. • Severely reduced kidney function (estimated glomerular filtration rate (eGFR) ≤ 29 mL/min/1.73 m^2). 12. Unstable weight (± 5%) over the last 6 months prior to Screening. 13. Type I diabetes or uncontrolled Type II diabetes (defined as HbAlc ≥ 10% at Screening.) 14. Total white blood cell (WBC) count < 2500/µL, or neutrophils < 1500/µL or hemoglobin < 8.5 g/dL at Screening. 15. Evidence of hepatic decompensation or severe liver impairment or cirrhosis, as defined by the presence of any of the following abnormalities: • Serum albumin < 3.2 mg/dL • INR > 1.3 • Total bilirubin > 1.3 mg/dL • AST > 5 × ULN [for elevation of ALT refer to inclusion criterion 7]

	• Alkaline phosphatase > 300 IU/L • Platelets outside of normal reference range (± 5%) • History of esophageal varices, ascites, or hepatic encephalopathy • Splenomegaly 16. History of liver transplantation or planned liver transplant. 17. History of biliary diversion. 18. Presence or history of other liver disease (including but not limited to autoimmune hepatitis, hereditary hemochromatosis, alpha-1-antitrypsin deficiency, Wilson's disease, drug-induced liver disease). 19. Current, or history of, significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females or more than 30 g/day in males, on average) or a score on the modified alcohol use disorders identification test (AUDIT) questionnaire ≥ 8. 20. History of bariatric surgery or intention to have bariatric surgery during study conduct. 21. 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 skin Bowen's disease, or basal cell carcinoma or actinic keratosis that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed). 22. 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 immunocompromise the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy. 23. Current severe progressive or uncontrolled disease, which in the judgment of the clinical investigator renders the subject unsuitable for the trial or puts the subject at increased risk. 24. 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. 25. Inability or unwillingness to undergo MRI of the abdomen (e.g., patients with pacemakers, or metal fragments / foreign objects in the body that are not compatible with performing an MRI of the abdomen, weight in excess of MRI machine capacity). 26. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins). 27. Ongoing participation (including safety follow-up period) in other interventional studies.

<table>
<tr><td>Study treatment</td><td>
<table>
<tr><th>Study treatment</th><th>Dose form</th><th>Route and frequency of administration</th></tr>
<tr><td>Investigational arm</td><td></td><td></td></tr>
<tr><td>Secukinumab 300 mg</td><td>2 × 150 mg PFS</td><td>s.c. weekly in first 4 weeks, followed by q4w up to Week 20.</td></tr>
<tr><td>Placebo</td><td>2 × Placebo PFS</td><td>s.c. at Week 13, 14, and 15.</td></tr>
<tr><td>Control arm</td><td></td><td></td></tr>
<tr><td>Placebo</td><td>2 x Placebo PFS</td><td>s.c. weekly in the first 4 weeks followed by q4w up to Week 8</td></tr>
<tr><td>Secukinumab 300 mg</td><td>2 x 150 mg PFS</td><td>s.c. weekly for 4 weeks starting at Week 12, followed by q4w up to Week 20</td></tr>
</table>
PFS = prefilled syringe, q4w = every 4 weeks, s.c. = subcutaneous
</td></tr>
<tr><td>Efficacy assessments</td><td>
• PASI
[redacted]
• Hepatic inflammation (assessed via liver enzyme levels)
[redacted]
</td></tr>
<tr><td>Key safety assessments</td><td>
• Adverse events (AEs)
• Vital signs
• Laboratory assessments (e.g. hematology, chemistry, urine tests)
• Physical examinations
</td></tr>
<tr><td>Other assessments</td><td>
• Alcohol use disorders identification test (AUDIT)
• Dermatology Life Quality Index (DLQI)
[redacted]
[redacted]
</td></tr>
<tr><td>Data analysis</td><td>The primary analysis will be performed comparing treatments with respect to the primary efficacy variable in a logistic regression model with the factors treatment group and center as factors and PASI score at Baseline (Day 1) as covariates. The odds ratio and its 95 % confidence interval (CI) and p-value will be given. The primary analysis will be based on the Full Analysis Set (FAS) and will be performed when all patients have completed the Week 12 assessment.</td></tr>
<tr><td>Key words</td><td>Plaque psoriasis, DLQI, [redacted], NAFLD, NASH, PASI, secukinumab</td></tr>
</table>

1 Introduction

1.1 Background

Psoriasis is a chronic, immune-mediated, inflammatory skin disease that affects approximately 2% to 3% of adults in the general population of Western countries (Mantovani et al 2016). Psoriasis is also frequently associated with multiple metabolic co-morbidities, including non-alcoholic fatty liver disease (NAFLD), obesity, type 2 diabetes, and metabolic syndrome (Boehncke and Schön 2015, Warnecke et al 2011). NAFLD affects up to 33% of the Western World population, where it has become an important public health problem due to its potential progression to severe liver disease (Weiss et al 2014). The pathogenesis of NAFLD is described by "multiple hits" on a non-alcoholic fatty liver (NAFL) which is a central feature of non-alcoholic steatohepatitis (NASH) (Jahn et al 2016). Histologically, NAFLD is defined by a spectrum of lesions, ranging from bland hepatic steatosis (defined as intrahepatic triglyceride content of more than 5% of the liver volume or liver weight) without inflammation or fibrosis (NAFL) to steatohepatitis (NASH), which involves hepatic inflammatory changes and apoptosis leading to liver injury and fibrosis.

The prevalence rate of hepatic steatosis is approximately 20-30% in non-obese patients but up to 75% in obese patients. Remarkably, in a cross-sectional study involving 103 United States middle-aged adult patients with psoriasis or psoriatic arthritis (Roberts et al 2015), the prevalence of ultrasound-diagnosed NAFLD was 47%, whereas that of NASH was 22% among those (n = 52) who underwent a liver biopsy. Recent studies document the prevalence of NAFLD to be around 50% in psoriasis patients (e.g. Gisondi et al 2009). A recent meta-analysis confirmed that psoriatic patients had a 2-fold increased rate of prevalent NAFLD compared with non-psoriatic control individuals, and that this risk was higher among those with either more severe psoriasis or psoriatic arthritis (Candia et al 2015). These data clearly indicate a prevalence of NAFLD in psoriasis patients, which is far above the general population. In addition, the psoriasis severity and systemic inflammatory load has been shown to be higher in patients with both psoriasis and NAFLD compared to psoriasis patients without NAFLD (Gisondi et al 2009).

Treatment options for psoriasis are classified as topical, phototherapy, conventional systemic or biologic therapy. Systemic drugs such as methotrexate, cyclosporine, fumarates, acitretin, apremilast and biologics such as tumor necrosis factor alpha (TNFα) antagonists (etanercept, adalimumab and infliximab), the anti-IL-12/23 monoclonal antibody ustekinumab, and the anti-IL-17 monoclonal antibody secukinumab are established therapies of moderate-to-severe psoriasis (Boehncke & Schön 2015, Nast et al 2015, Nast et al 2017). Secukinumab was shown to be effective in moderate to severe psoriasis in a large Phase 2/3 clinical trial program, validating IL-17A as a therapeutic target for psoriasis (Langley et al 2014). Secukinumab was approved in 2015 by the United States federal Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy.

No medical therapy has been established or licensed for NAFLD at this time. Different T-cell populations such as T regulatory (Tregs), Th1 and Th17 cells play a central role in the immunopathogenesis of fatty liver disease (Vonghia et al 2013). Th17 cells lead to tissue

inflammation by the secretion of various cytokines such as IL-17, IL-21, IL-22 and TNFα (Ouyang and Valdez 2008). Following the recruitment of macrophages and release of pro-inflammatory cytokines in early NASH, induction of hepatic Th17 cell infiltration has recently been described as a pathophysiological hallmark in human NASH (Tang et al 2011, Rau et al 2016, Harley et al 2014). The pathophysiological relevance of IL-17 becomes evident from studies in IL-17RA-/- mice, which are resistant to the development of steatohepatitis, whereas wild-type mice show progression from NAFL to NASH by induction of the IL-17 axis (Harley et al 2014, Kisseleva et al 2014). Moreover, in a murine high fat-induced NAFLD model IL-17 blockade with monoclonal IL-17 antibody showed an improved liver function, attenuated hepatic lipid accumulation, suppressed Kupffer cell activation and decreased proinflammatory cytokine levels (Xu et al 2013). IL-17, therefore, represents an attractive therapeutic target for NAFLD (Giles et al 2015).

Given the frequent co-incidence of NAFLD and psoriasis, and the higher psoriasis severity and increased inflammatory load in patients with both psoriasis and NAFLD compared with patients with psoriasis only (Gisondi et al 2009), the efficacy of secukinumab in psoriasis patients with coexisting NAFLD remains to be further investigated. With IL-17 being a shared pathophysiological hallmark of both psoriasis and NAFLD, this study will further explore whether patients with psoriasis and NAFLD additionally benefit from a treatment with secukinumab beyond their skin.

1.2 Purpose

The aim of this study is to assess the therapeutic efficacy of secukinumab on the psoriatic skin and to explore the anti-inflammatory (reduction of hepatic inflammation and cell damage), anti-steatotic (reduction of hepatic triglyceride content) and anti-fibrotic (reduction of hepatic fibrosis) effects of secukinumab in patients with psoriasis and coexisting NAFLD.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary objectives	**Endpoints for primary objectives**
• To demonstrate superiority of secukinumab compared to placebo in patients with moderate to severe chronic plaque-type psoriasis and NAFLD with respect to PASI90 response at Week 12.	• Proportion of patients achieving PASI90 response at Week 12.
Secondary objectives	**Endpoints for secondary objectives**
• To evaluate the effect of secukinumab compared to placebo on hepatic inflammation in patients with moderate to severe psoriasis and NAFLD with respect to serum ALT levels at Week 12.	• Serum ALT level at Week 12.
• To evaluate the effect of secukinumab compared to placebo on quality of life	• Proportion of patients achieving DLQI 0/1 at Week 12.

Objectives	Endpoints
in patients with moderate to severe psoriasis and NAFLD with respect to DLQI at Week 12	
[redacted]	

AE = adverse event, AESI = adverse events of special interest, ALT = alanine aminotransferase, [redacted], DLQI = dermatology life quality index, [redacted],

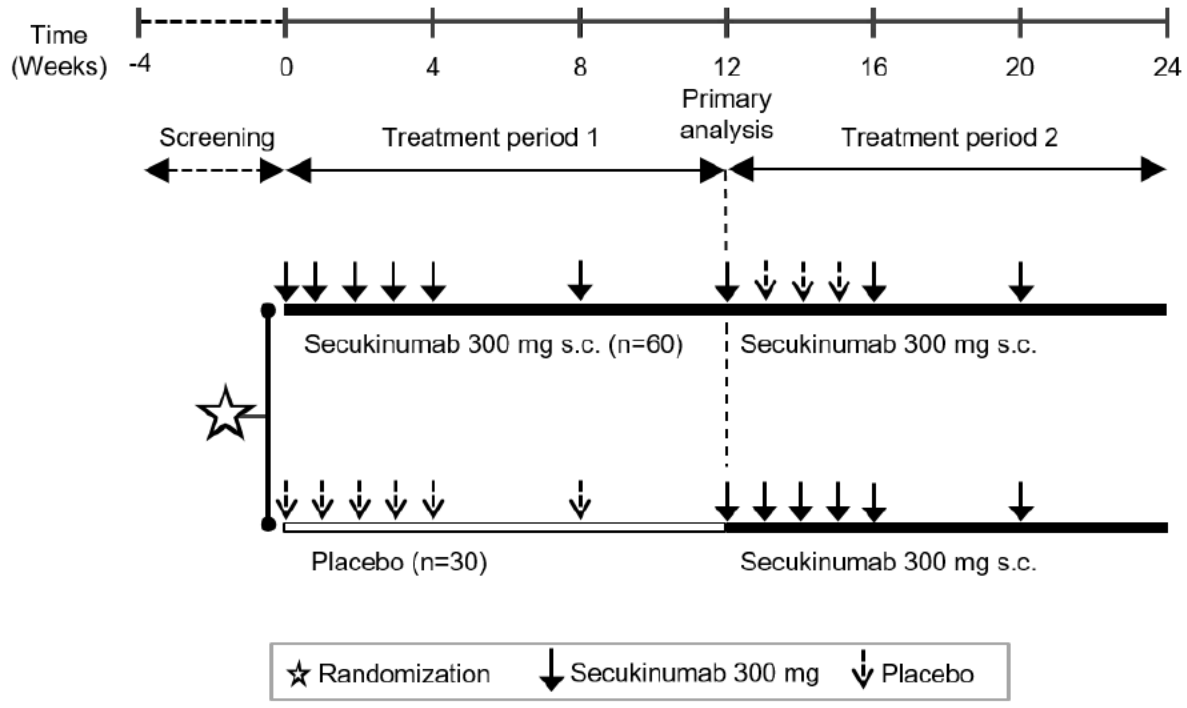
Objectives	Endpoints
[redacted], NAFLD = non-alcoholic fatty liver disease, NASH = non-alcoholic steatohepatitis, PASI90 = psoriasis area and severity index, SAE = serious adverse event.	

3 Study design

This is a randomized, placebo-controlled, double-blind, parallel-group, interventional, multicenter study in patients with moderate to severe plaque psoriasis and coexisting NAFLD. The study consists of 3 periods:

- **Screening Period**: patient eligibility will be assessed and prohibited medication will be tapered during the max. 4-week Screening Period prior to Randomization/Baseline.
- **Treatment Period 1 (Baseline to Week 12)**: patients will be randomized 2:1 to either receive secukinumab 300 mg s.c. (in 2 × 150 mg PFS) or placebo (in 2 × PFS) at Randomization/Baseline, Week 1, Week 2, Week 3, Week 4 and Week 8.
- **Treatment Period 2 (Week 12 to Week 24)**: starting from Week 12, all patients will receive secukinumab 300 mg s.c. up to Week 20. Patients who were randomized to placebo during Treatment Period 1 will receive secukinumab 300 mg s.c. at Week 12, Week 13, Week 14, Week 15, Week 16 and Week 20. Patients who were randomized to secukinumab during Treatment Period 1 will receive secukinumab 300 mg s.c. at Week 12, Week 16 and Week 20, and placebo at Week 13, Week 14 and Week 15 to maintain the blind.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

The randomized, double-blind, parallel-group design of this study is aligned with previous studies performed in the indication of plaque psoriasis and registration secukinumab studies. The double-blind design will be maintained throughout the study to ensure reliable efficacy and safety measures are obtained for both treatment groups in patients with moderate to severe plaque psoriasis and coexisting NAFLD. This study involves 2 treatment periods, which will allow exploration of efficacy and safety effects of secukinumab 300 mg up to Week 12 in a placebo-controlled manner and additionally from Week 12 up to Week 24 (with last dose at Week 20) with active treatment only.

4.2 Rationale for dose/regimen and duration of treatment

Secukinumab 300 mg s.c. with an initial weekly induction schedule up to 4 weeks followed by a s.c. administration of every 4 weeks up to Week 20 is based on the secukinumab Phase 3 registration program.

The 12-week placebo-controlled Treatment Period 1 will allow indirect comparisons to placebo-controlled pivotal studies regarding skin-related endpoints which also had their primary endpoint at Week 12 and assessment of effects on NAFLD related endpoints exceeding typically observed placebo effects (Neuschwander-Tetri et al 2015, Ratziu et al 2008, Harrison et al 2018a, Harrison et al 2018b).

In previous proof-of-concept studies in NASH patients, 12 weeks has been a standard treatment length to demonstrate reduction of hepatic inflammation, steatosis and fibrosis markers, and effects have been observed as early as after 4 weeks of treatment (Neuschwander-Tetri et al 2015, Ratziu et al 2008, Harrison et al 2018a, Harrison et al 2018b). As due to ethical reasons, the placebo-controlled period needs to be limited to 12 weeks in patients with moderate to severe psoriasis, Treatment Period 2 will enable this study to explore the longitudinal effects of secukinumab up to 24 weeks. Moreover, with Treatment Period 2, all patients enrolled in the study will be able to benefit from secukinumab treatment.

4.3 Rationale for choice of control drug (placebo)

A placebo control has been selected for the first 12 weeks in this study in order to assess the safety and effectiveness of secukinumab 300 mg in a double-blind, unbiased manner in patients with moderate to severe psoriasis and concomitant NAFLD. Patients assigned to placebo will switch to active treatment with secukinumab 300 mg for Treatment Period 2 (Week 12 up to Week 20). Furthermore, patients will be allowed to use concomitant potent topical corticosteroids and/or vitamin D analogues as needed at the discretion of the investigator.

4.4 Purpose and timing of primary analysis/design adaptations

The primary analysis for this study will be conducted after all patients have completed Treatment Period 1. Following an evaluation of these data by a Study Steering Committee, it

will be decided whether the study will be amended to include an additional part enrolling patients with NAFLD without coexisting psoriasis.

4.5 Risks and benefits

Based on the therapeutic efficacy and safety in 4 pivotal randomized Phase 3 studies with dosages of 300 mg or 150 mg (Langley et al 2014, Blauvelt et al 2015, Paul et al 2015, Thaci et al 2015) secukinumab was approved to treat adults with moderate-to-severe plaque psoriasis by the FDA and the EMA in 2015. Nasopharyngitis, headache, and upper respiratory tract infection were the most common AEs and were more frequent in the secukinumab arms (mostly mild or moderate). Injection-site reactions were rare and mostly mild or moderate. A similar safety profile has been obtained with dosages of 300 mg, 150 mg or 75 mg secukinumab in a randomized Phase 3 trial in patients with psoriatic arthritis (Mease et al 2015, Mc Innes et al 2015). No cumulative or unexpected safety concerns have been identified through 5 years of treatment in the extension phase of the SCULPTURE study (Bissonnette et al 2015). Overall, serious adverse events (SAEs) occurred at similar low incidences across treatments during the first 12-week and the entire 52-week treatment periods in a pooled analysis of 10 Phase 2 and 3 studies with few AEs leading to discontinuation (Van de Kerkhof et al 2016).

Although not pre-specified in the trial protocols for secukinumab above it can be assumed from the epidemiological association that a substantial proportion of the recruited psoriasis patients suffered from concomitant NAFLD. When reported, a mean body mass index (BMI) of 28-34 kg/m^2 clearly illustrates the dysmetabolic condition of the included patients (Langley et al 2014, Paul et al 2015, Thaci et al 2015). No major liver-related events or deterioration in liver laboratory assessments have been reported to date in Phase 2 and 3 secukinumab trials. With this information from almost 4000 psoriasis patients, half of them putatively with concomitant NAFLD, it appears acceptable to rate the risk of unexpected AEs or SAEs as relatively low. In addition, one preclinical study shows that IL-17 inhibits adipogenesis, moderates adipose tissue accumulation and contributes to control glucose metabolism at least in mice und high fat diet (Zuniga et al 2010).

Fatty liver disease represents a globally increasing health threat. In particular, steatohepatitis (NASH) with accompanying inflammation contributes to the development of progressive liver damage and sometimes end stage liver failure. End stage liver damage is characterized by the development of liver cirrhosis and hepatocellular carcinoma (HCC) as the most life-threatening complication. There is no established therapy with proven long-term success and absent risk profile so far. Given the fact that a therapy with secukinumab in a dosage

according to the label represents a convenient and safe intervention in patients with plaque psoriasis, the conduction this study in psoriasis patients with concomitant NAFLD is justified to treat a frequently coinciding disease of global socioeconomic impact and disease burden with life-threatening complications of end stage disease.

The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

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

5 Population

Approximately 90 patients with moderate to severe plaque psoriasis and coexisting NAFLD who are candidates for systemic psoriasis therapy will be included in this study.

5.1 Inclusion criteria

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

1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study, and must provide written, signed and dated informed consent before any study assessment is performed.
2. Men and women ≥ 18 years of age at the time of consent.
3. Moderate to severe plaque-type psoriasis diagnosed for at least 6 months prior to Screening with a PASI of >10 at baseline.
4. Candidate for systemic therapy, defined as a subject having moderate to severe chronic plaque-type psoriasis that is inadequately controlled by:
   - Topical treatment and/or,
   - Phototherapy and/or,
   - Previous systemic therapy.
5. Diagnosis of NAFLD by either ultrasound at Screening or liver histology within 6 months before Baseline.
6. Obesity with BMI > 25 kg/ m^2 at Screening.
7. Elevation of ALT 1.2 to 3.0 × ULN.
8. Liver fat ≥ 8% at Screening as determined by the reading of the central MRI vendor of locally produced images. Note: the MRI assessment should only be performed after eligibility has been confirmed for all other Screening assessments.

5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study.

1. Forms of psoriasis other than chronic plaque-type psoriasis at Screening.

2. Drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium) at screening and baseline.
3. Ongoing use of prohibited treatments (see Section 6.2.2). Respective washout periods detailed in this section have to be adhered to.
4. History of hypersensitivity to any of the study drug constituents.
5. Pregnant or nursing (lactating) women.
6. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the study or longer if required by locally approved prescribing information (e.g., 20 weeks in the European Union). Effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
   - Male sterilization (at least 6 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
   - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps). For countries where applicable, the use of spermicidal foam/gel/film/cream/vaginal suppository will be allowed.
   - Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system or other forms of hormonal contraception that have comparable efficacy (failure rate < 1 %), for example hormone vaginal ring or transdermal hormone contraception.

     In case of use of oral contraception, women should have been stable on the same pill for a minimum of 12 weeks before taking study treatment.

     Women are considered post-menopausal and not of childbearing 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 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment, is she considered not of childbearing potential.
7. Previous treatment with biological drug targeting IL-17 or the IL-17 receptor (including prior treatment with secukinumab, ixekizumab, or brodalumab).
8. Past medical history record of infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C prior to screening.
9. Active systemic infections during the last two weeks (exception: common cold) prior to randomization or any infection that reoccurs on a regular basis.
10. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuantiFERON-TB Gold Plus (QFT) test at screening.

Subjects with a positive or indeterminate QFT test may participate in the study if full tuberculosis work up (according to local practice/guidelines) was completed within 12 weeks prior to randomization and establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to local guidelines must have been completed prior to screening. During treatment of latent tuberculosis, ALT had to remain below 2x compared to pre-treatment ALT value.

11. Significant medical problems, including but not limited to:
    - Congestive heart failure [New York Heart Association status of class III or IV].
    - Severely reduced kidney function (estimated glomerular filtration rate (eGFR) $\leq$ 29 mL/min/1.73m^2).
12. Unstable weight (± 5%) over the last 6 months prior to Screening.
13. Type I diabetes, or uncontrolled Type II diabetes (defined as HbAlc $\geq$ 10 % at screening).
14. Total white blood cell (WBC) count < 2500/µL, or neutrophils < 1500/µL or hemoglobin < 8.5 g/dL at Screening.
15. Evidence of hepatic decompensation or severe liver impairment or cirrhosis, as defined by the presence of any of the following abnormalities:
    - Serum albumin < 3.2 mg/dL
    - INR > 1.3
    - Total bilirubin > 1.3 mg/dL
    - AST > 5x ULN [for elevation of ALT refer to inclusion criterion 7]
    - Alkaline phosphatase > 300 IU/L
    - Platelets outside of normal reference range (± 5%)
    - History of esophageal varices, ascites, or hepatic encephalopathy
    - Splenomegaly
16. History of liver transplantation or planned liver transplant.
17. History of biliary diversion.
18. Presence or history of other liver disease (including but not limited to autoimmune hepatitis, hereditary hemochromatosis, alpha-1-antitrypsin deficiency, Wilson's disease, drug-induced liver disease).
19. Current, or history of, significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females or more than 30 g/day in males, on average) or a score on the modified alcohol use disorders identification test (AUDIT) questionnaire $\geq$ 8.
20. History of bariatric surgery or intention to have bariatric surgery during study conduct.
21. 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 skin Bowen's disease, or basal cell carcinoma or actinic keratosis that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).

22. 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 immunocompromise the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy.
23. Current severe progressive or uncontrolled disease, which in the judgment of the clinical investigator renders the subject unsuitable for the trial or puts the subject at increased risk.
24. 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.
25. Inability or unwillingness to undergo MRI of the abdomen (e.g., patients with pacemakers, or metal fragments / foreign objects in the body that are not compatible with performing an MRI of the abdomen, weight in excess of MRI machine capacity).
26. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
27. Ongoing participation (including safety follow-up period) in other interventional studies.

No additional exclusions may be applied by the Investigator in order to ensure that the study population will be representative of all eligible patients.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drug

The investigational and control arm regimens are presented in Table 6-1.

Table 6-1 Investigational and control drug

Study treatment (Name and strength)	Pharmaceutical dosage form	Route and frequency of administration	Supply type	Sponsor (global or local)
Investigational arm				
Secukinumab 300 mg	2 × PFS	s.c. weekly in first 4 weeks, followed by q4w up to Week 20	Double-blind supply; PFS	Sponsor (local)
Placebo	2 × PFS	s.c. at Week 13, 14, 15 to maintain the blind	Double-blind supply; PFS	Sponsor (local)
Control arm				
Placebo	2 x PFS	s.c. weekly in the first 4 weeks followed by q4w up to Week 8	Double-blind supply; PFS	Sponsor (local)
Secukinumab 300 mg	2 x PFS	s.c. weekly for 4 weeks starting at Week 12, followed by q4w up to Week 20	Double-blind supply; PFS	Sponsor (local)

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

Treatment period 1

Patients will be randomized 2:1 to either receive secukinumab 300 mg s.c. (in 2 × 150 mg PFS) or placebo at randomization, Week 1, Week 2, Week 3, Week 4 and Week 8.

Treatment period 2

Starting from Week 12, all patients will receive secukinumab 300 mg s.c. up to Week 20. Patients who were randomized to receive placebo during Treatment Period 1 will receive secukinumab 300 mg s.c. at Week 12, Week 13, Week 14, Week 15, Week 16 and Week 20 Patients who were randomized to receive secukinumab during Treatment Period 1 will receive secukinumab 300 mg s.c. at Week 12, Week 16 and Week 20, and placebo at Week 13, Week 14 and Week 15 to maintain the blind.

6.1.4 Treatment duration

This is a 24-week study. Patients will receive either secukinumab or placebo (2:1 ratio) for the first 12 weeks of the study (last study drug injection at Week 8), then secukinumab or secukinumab with intermittent placebo (placebo only at Week 13, 14 and 15 in patients randomized to receive secukinumab during Treatment Period 1) for the next 12 weeks of the study (last study drug injection at Week 20).

6.2 Other treatments

6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient is enrolled into the study must be recorded on the appropriate CRFs.

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. If the patient is already enrolled, contact Novartis to determine if the patient should continue participating in the study.

Patients will be permitted to take concomitant potent topical corticosteroids and/or vitamin D analogues as needed at the discretion of the investigator over the course of the study, according to the respective approved label.

6.2.2 Prohibited medication

Use of any treatments displayed in Table 6-2 that could confound the efficacy and safety of the study treatment are NOT allowed during the study after Baseline (Day 1) for any indication; wash-out periods for these treatments are indicated in the table. If the use of these treatments is required, then the patient should **NOT** be randomized into the study.

The Investigator should instruct the patient to notify the study site about any new treatments he/she takes after the start of study treatment. All prohibited medications and significant

non-drug therapies administered after the patient starts treatment with study treatment must be listed on the CRF.

If a prohibited treatment listed in Table 6-2 is used during the study, the patient should discontinue use of the prohibited treatment if he/she wishes to continue in the study.

At the discretion of the Investigator, if the patient's use during the study of a prohibited treatment listed in Table 6-2 presents undue safety risk for the patient, the patient should be discontinued from study treatment as per Section 9.1.1.

If the patient received a live virus vaccination during the study, the patient must discontinue study treatment.

Table 6-2 Prohibited medication

Prohibited treatments †, ‡	**Wash-out period (before first study drug administration)**
Biological drug targeting IL-17 or the IL-17 receptor (other than secukinumab e.g. ixekizumab, brodalumab)	No prior use allowed
Secukinumab	No prior use allowed
Biological immunomodulating agents other than above (e.g. etanercept, infliximab, adalimumab, alefacept, briakinumab, ustekinumab)	12 weeks
Methotrexate	8 weeks
Other systemic immunomodulating treatments (e.g. cyclosporine A, corticosteroids*§, cyclophosphamide).	4 weeks
Other systemic psoriasis treatments§ (e.g. retinoids, fumarates, apremilast).	4 weeks
Photochemotherapy (e.g. PUVA)	4 weeks
Phototherapy (e.g. UVA, UVB)	2 weeks
Topical treatment that is likely to impact signs and symptoms of psoriasis (vitamin D analogues, tacrolimus, pimecrolimus, potent corticosteroids, salicylvaseline, salicylic acid, lactic acid, tar, alpha-hydroxy or fruit acids) Potent topical corticosteriods and/or vitamin D analogues are allowed after baseline as needed at the discretion of the investigator.	2 weeks
Live virus vaccinations (including nasal-spray flu vaccine)	6 weeks
Any other investigational treatment	4 weeks or 5 half-lives (whichever is longer)
Obeticholic acid	4 weeks
Pharmacologically-active weight loss medications (for example; lorcaserin, phentermine/topiramate, bupropion-naltrexone HCl, orlistat)	4 weeks
Anti-diabetic medications, insulin, beta-blockers, thiazide diuretics, fibrates, statins, niacin, ezetimibe, thyroid hormone, psychotropic	Not allowed UNLESS on stable dosing for at least 3 months

medications, estrogen or estrogen containing birth control.	before randomization
Vitamin E, if doses > 200 IU/day (≤ 800 IU/day)	Not allowed UNLESS on stable dosing for at least 3 months before randomization.
Vitamin E doses > 800 IU/day	3 months
Glitazone, liraglutide or ursodeoxycholic acid (UDCA) therapy	Not allowed if initiated within 3 months before baseline

UVA = ultraviolet A, UVB = ultraviolet B, MTX = methotrexate, PUVA = psoralen and UVA

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

‡ In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator and after consultation with Novartis. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

* Inhaled corticosteroids with only a topical effect (e.g. to treat asthma) are not considered "systemic immunomodulating treatments" and are therefore acceptable as a co-treatment.

§ There is no restriction on the use of anti-histamines or of corticosteroid drops used in the eye or ear if dose regimen is stable for at least 4 weeks before the first study treatment administration.

6.2.3 Rescue medication

Rescue medication for psoriasis is not permitted in this study.

6.2.4 Dietary restrictions

No alcohol consumption is allowed for 8 hours before each dose of study medication. Alcohol should also not be consumed for 8 hours before each study visit.

To keep the fat intake as constant as possible, patients participating in this study will be instructed to carefully adhere to American Heart Association (AHA) diet or local equivalent if there is a country specific recommended diet (Appendix 2). Patients will be asked about dietary compliance to the AHA diet (or local equivalent) as outlined in Table 8-1.

6.3 Patient numbering, treatment assignment, randomization

6.3.1 Patient numbering

Germany

Each patient is identified in the study by a Patient ID (Patient ID) that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient ID consists of the Center Number (Center No.) (ascending numbers starting with 1001, as assigned by Novartis to the investigative site) with a sequential Patient Number (Patient No.) suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the ICF, the patient is assigned to the next sequential Patient No. available in this center by the investigator. At each site the first patient is assigned Patient No. 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned Patient No. 2, the third patient is assigned Patient No. 3). Once assigned to a patient, a Patient No. 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.

Spain

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 ICF, the patient is assigned to the next sequential Patient No. available in this center by the investigator. At each site the first patient is assigned Patient No. 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned Patient No. 2, the third patient is assigned Patient No. 3). The subject number (patient ID) is assigned, at Screening Visit 1, via Interactive Response Technology (IRT).

The Patient ID consists of the Center Number (Center No.) (ascending numbers starting with 2001, as assigned by Novartis to the investigative site) with a sequential Patient Number (Patient No.) suffixed to it, so that each patient is numbered uniquely across the entire database.

Once assigned to a patient, a Patient No. 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.

6.3.2 Treatment assignment, randomization

Germany

At Baseline (Randomization Visit/Day 1), all patients who meet the inclusion criteria and do not fulfill any of the exclusion criteria will be given the lowest available number of the randomization block assigned to each site. This number assigns them to one of the treatment arms. The investigator will enter the randomization number on the eCRF.

The randomization numbers will be generated using the following procedure to insure that treatment assignment is unbiased and concealed from patients and investigator staff. A randomization list will be produced by or under the responsibility of Novartis using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

The randomization scheme will be reviewed by a Biostatistics Quality Assurance Group and locked by them after approval.

Spain

At Baseline (Randomization visit /Day 1), all patients who meet the inclusion criteria and do not fulfill any of the exclusion criteria will be randomized via IRT and a treatment will be assigned to individual subjects by way of a randomization number. The randomization number is only used to identify which treatment the patient has been randomized to receive. The patient number assigned to a patient at screening remains the unique identifier for the patient throughout the study.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff.

A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers.

These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug.

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

6.4 Treatment blinding

Patients, Investigator staff, persons performing the assessments, and the Clinical Trial Team will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study.
2. The identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Unblinding will occur in the case of patient emergencies and at the conclusion of the study.

A selected Novartis clinical team will be unblinded to the Week 12 results at the time of primary analysis. Details will be specified in a separate document.

6.5 Dose escalation and dose modification

Study treatment dose adjustments are not permitted. Study treatment interruption should be avoided with the following exceptions:

Study treatment interruption is only permitted if, in the opinion of the investigator, a patient is deemed to be placed at a significant safety risk unless dosing is temporarily interrupted. In such cases study treatment should be interrupted only during the time that this risk is present and ongoing. Study treatment can be restarted at the next scheduled visit after resolution of the safety risk.

Any study treatment interruption must be recorded on the corresponding CRF page.

6.5.1 Follow-up for toxicities

Not applicable.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

All doses of study treatment administration will be recorded on the appropriate Dosage Administration Record CRF. Compliance to the planned administration schedule is expected to be high since the administrations of study treatment will be done in the presence of the Investigator or study personnel. Compliance will also be assessed by means of site and patient-specific drug accountability by Novartis study personnel during the site monitoring visits using medication pack numbers, Drug Label Form information.

6.6.2 Emergency breaking of assigned treatment code

Emergency unblinding should only be done when necessary in order to treat the patient. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Two complete sets of emergency code break cards are provided by Novartis. One set of emergency code break cards is provided by Novartis and is to be distributed to the investigators. They must be stored in a secure place but accessible in case of emergency. The investigator will receive a blinded code break card for each patient, with the details of drug treatment covered by a sealed tear-off cover. In an emergency, the tear-off cover can be removed to determine the treatment. The tear-off covers are not to be removed for any reason other than an emergency. When the investigator removes the tear-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. The unblinded treatment code should not be recorded on the eCRF. The investigator must also immediately inform the Novartis monitor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the code break cards in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study drug name if available, patient number, and instructions for contacting the German Novartis affiliated company (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable.

[redacted]

Spain

Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

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

- protocol number
- subject number

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

The unblinded treatment code should not be recorded on the eCRF. The investigator must also immediately inform the Novartis monitor that the code has been broken.

6.7 Preparation and dispensation

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

Germany

The randomization number will be printed on the study medication label.

As per the treatment assigned to the patient, investigator staff will select the study treatment to dispense to the patient. The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

Two treatment packages (i.e. 1 package for Treatment Period 1 and 1 package for Treatment Period 2) will be supplied for each patient, with each package containing sufficient study treatment for all visits in each period (i.e. 2 × PFS labelled for each treatment visit).

Spain

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

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

Medication labels will be in the local language and comply with the local legal requirements.

For **Germany**, they will include storage conditions for the study treatment but no information about the patient except for the randomization number. For **Spain,** they will include storage conditions for the study treatment and medication number.

The Investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Note: all injections of secukinumab/placebo will be administered by site staff or under supervision of site staff at the scheduled treatment visits.

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

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

Secukinumab solution for s.c. injection or placebo solution will be provided in PFS as described in Section 6.7.

Each patient will require 1 box (containing 2 × PFS) for each treatment visit throughout the study, i.e.

- Two secukinumab 150 mg PFS **OR**
- Two secukinumab placebo 150 mg PFS.

Patients assigned to the investigational arm will receive secukinumab 300 mg weekly for the first 4 weeks, followed by q4w up to Week 20, and placebo to secukinumab at Week 13, 14 and 15.

Patients assigned to the control arm will receive placebo to secukinumab weekly for the first 4 weeks, then at Week 8, followed by secukinumab 300 mg weekly for 4 weeks starting from Week 12, then q4w up to Week 20.

For German sites all study treatment kits assigned to the patient during the study will be captured in the eCRF. For Spanish sites, no kit numbers will be captured.

Administration

All doses of study treatment that are administered at the study site should be performed after the study assessments for the visit, including blood sampling and PRO questionnaires, have been completed.

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

Prior to administration, the boxes containing the PFS with study treatment solution should be allowed to come to room temperature unopened. Used PFS should be disposed immediately after use in a sharps container **OR** according to local regulations.

The study treatment solution must be injected s.c. in non-affected areas of the skin. If possible throughout the trial, the study treatment should be administered to one of the following body regions, rotating the injection site from visit to visit: right thigh, left thigh, right stomach, left stomach, upper outer arm (when assisted by attendant).

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

7 Informed consent procedures

Eligible patients may only be included in the study after providing, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

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 an ICF that complies with the ICH GCP guidelines and local regulatory requirements and is considered appropriate for this study.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (and/or Core Data Sheet for marketed drugs). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between Investigator's Brochure 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 then must be discussed with the patient.

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

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Recommended study visit windows are ± 2 days for Week 1, 2, 3, 4, 8, 12, 13, 14, 15, and 16, ± 3 days for Week 20 and 24. [redacted]

Patients who prematurely discontinue the study treatment (s.c. secukinumab or placebo) are encouraged to remain in the study to continue the study-related assessments until completion of the study.

Patients who prematurely discontinue completely from the study for any reason should return for the final visit to undergo the EOT assessments (4 weeks after the last study treatment administration of secukinumab). This will be EOT1 (Week 12) for patients who prematurely discontinue during Treatment Period 1 and EOT2 (Week 24) for patients who prematurely discontinue during Treatment Period 2. See Section 9.1.1 for further details.

At this visit, all dispensed investigational product should be reconciled, and the AE and concomitant medications recorded on the CRF.

If a patient refuses to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone or by sending appropriate correspondence (i.e. certified letter) immediately. At this contact, the safety (e.g. potential occurrence of AE or SAE) and the primary reason for a patient's premature withdrawal should be determined.

At a minimum, patients who prematurely discontinue the treatment will be contacted for safety evaluations during the 4 weeks following the last dose of study treatment, including final contact at the 4 week point. Documentation of attempts to contact the patient should be recorded in the subject record.

Table 8-1 Assessment schedule

	Screening[§]		Baseline	Treatment Period 1					Treatment Period 2							
Week (relative to baseline)	**-4 to -1**		**BSL**	**1**	**2**	**3**	**4**	**8**	**12 EOT1**	**13**	**14**	**15**	**16**	**20**	**24 EOT2**	**Uns[§§]**
Day	**-28 to -7**		**1**	**8**	**15**	**22**	**29**	**57**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	
[§] The second screening visit can be conducted as soon as eligibility has been confirmed for all assessments from the first screening visit. [§§] 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.																
Obtain informed consent	X															
Demographics	X															
Inclusion/exclusion criteria: These assessments are supported by and stored within the source documentation. Data relating to inclusion/exclusion criteria are captured in the corresponding CRF	X		X													
Smoking history	X															
Psoriasis medical history / Previous psoriasis therapies	X															
Other medical history and prior treatments	X															
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening[§]		Baseline	Treatment Period 1					Treatment Period 2							
Week (relative to baseline)	**-4 to -1**		**BSL**	**1**	**2**	**3**	**4**	**8**	**12 EOT1**	**13**	**14**	**15**	**16**	**20**	**24 EOT2**	**Uns[§§]**
Day	**-28 to -7**		**1**	**8**	**15**	**22**	**29**	**57**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	
Alcohol history (AUDIT)/compliance	X		X						X						X	X
Physical examination	S		S												S	S
Height	X															
Weight	X		X	X	X	X	X	X	X				X	X	X	X
Body mass index	X															
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist and hip circumference	X		X						X						X	X
Blood collection for:																
Routine laboratory assessments including analysis of liver enzymes ([redacted], ALT, [redacted] [redacted])	C		C		C		C	C	C				C	C	C	C
Coagulation (INR)	C															
QuantiFERON-TB Gold Plus test	C															C
Serum pregnancy test for females of childbearing potential	C															C
Follicle stimulating hormone (FSH) test (if applicable)	C															
[redacted]																

	Screening[§]	Baseline	Treatment Period 1						Treatment Period 2						
Week (relative to baseline)	**-4 to -1**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12 EOT1**	**13**	**14**	**15**	**16**	**20**	**24 EOT2**	**Uns[§§]**
Day	**-28 to -7**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	
[redacted]															
Urine pregnancy test (local)			X					X						X	X
Urinalysis (local)			X					X						X	X
PASI/BSA	X		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]															

	Screening[§]		Baseline	Treatment Period 1					Treatment Period 2							
Week (relative to baseline)	**-4 to -1**		**BSL**	**1**	**2**	**3**	**4**	**8**	**12 EOT1**	**13**	**14**	**15**	**16**	**20**	**24 EOT2**	**Uns[§§]**
Day	**-28 to -7**		**1**	**8**	**15**	**22**	**29**	**57**	**85**	**92**	**99**	**106**	**113**	**141**	**169**	
DLQI	X		X				X	X	X				X	X	X	X
[redacted]																
(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	X	X		
Drug accounting			X	X	X	X	X	X	X	X	X	X	X	X		
AHA diet review			S				S		S				S		S	
Diet compliance			X						X						X	

[redacted], ALT = alanine aminotransferase, [redacted], BSA = body surface area, EOT = end of treatment period; [redacted] PASI = psoriasis area and severity index
C = centrally analyzed laboratory or MRI; X = assessment to be recorded on clinical database; S = assessment to be recorded on source documentation

8.1 Screening

Patient's eligibility for the study will be assessed during Screening period (Day -28 to -7) including Screening Visit 1, Screening Visit 2 and at the Baseline Visit (see Table 8-1).

It should be noted that for each patient, results from Screening Visit 1 must be available and indicate primary eligibility before the patient can proceed to Screening Visit 2.

Patients who fail screening for any reason may be rescreened. If the reason for screen failure is regarded as a transient constraint for study participation, then there will be no restriction on the number of times a potential patient may be rescreened or on how much time must pass from the date of screen failure and the date of rescreening. Patients who are rescreened must sign a new ICF and be issued a new Patient No. before any study-related assessment is performed or any data for the Screening Period are collected for the patient under the new Patient No.

The Investigator or qualified site staff will record all rescreenings on the Rescreening eCRF page and any applicable screening numbers the patient was issued prior to the current screening number. The date of the new informed consent signature must be entered on the Informed Consent eCRF page to correspond with the new screening Patient No.

The Withdrawal of Consent eCRF page must be completed if consent was withdrawn during the Screening Period before the patient was randomized.

8.1.1 Information to be collected on screening failures

Patients who sign an ICF and subsequently are found to be ineligible prior to randomization will be considered screen failures. The reason for screen failure should be recorded on the appropriate eCRF page. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failures. No other data will be entered into the clinical database for screen failures, unless the patient experienced an SAE during the Screening Period (see Section 10.1.3 for reporting details). If the patient fails to be randomized, Novartis (Germany) / the IRT (Spain) must be notified within 2 days.

8.2 Patient demographics/other baseline characteristics

Baseline assessments will occur during Screening Visits or the Baseline Visit depending on the assessment as indicated in Table 8-1.

Patient demographics and Baseline characteristics to be collected for all patients include: year of birth, age, sex, race, height, weight.

8.2.1 Smoking history

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

8.2.2 Tuberculosis screening

A central laboratory immunological test (QuantiFERON-TB Gold Plus) must be performed at Screening to screen the patient population for latent tuberculosis infection. The results must be known prior to randomization to determine the patient's eligibility for the study.

Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that:

The patient has no evidence of active tuberculosis.

If presence of latent tuberculosis is established then treatment according to local country guidelines must have been completed before screening.

The QuantiFERON-TB Gold Plus test will be analyzed by the central laboratory. Details on the collection, processing and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

8.2.3 Relevant medical history/current medical conditions

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

Patients with inflammatory bowel disease will be eligible for the study but should be closely followed when (possibly) treated with secukinumab.

8.2.3.1 Psoriasis medical and treatment history

Disease history will be collected at Screening Visit 1. The information to be collected and entered in the Psoriasis History eCRF page and Prior Psoriasis Therapies eCRF page will include the following:

- Date of first diagnosis of plaque psoriasis.
- Previous treatments of psoriasis (including previous use of biologic therapies, as well as phototherapy and/or photo-chemotherapy) and the reason for discontinuation of each therapy.
- Presence of psoriatic arthritis or ankylosing spondylitis (including questions on signs and symptoms captured in the eCRF) and the date of the first diagnosis by a physician.

8.2.4 Prior and concomitant medications

Concomitant medications and prior non-psoriasis medications taken within the 6 months preceding study enrollment will be captured at Screening Visit 1, and updated at the Baseline Visit or subsequent visits.

8.2.5 Serum pregnancy test

A serum pregnancy test will be performed for females of childbearing potential at Screening Visit 1.

8.2.6 Other baseline characteristics

Other Baseline characteristics will be collected as described in Section 8.3 and Section 8.4.

8.3 Efficacy

- PASI

[redacted]

- Hepatic inflammation (assessed via liver enzyme levels)

[redacted]

8.3.1 Psoriasis area severity index

The Investigator or trained qualified designee will complete the PASI assessment as indicated in Table 8-1. Whenever possible, the same evaluator should perform this PASI 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 PASI assessment). The following calculations will be done: each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added up to estimate the total BSA affected by plaque-type psoriasis. The PASI scoring system is further described in Table 8-2.

A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2006) will be derived as indicated in Table 8-2. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

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.

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

Table 8-2 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	0=none 1=slight 2=moderate 3=severe	0=none 1=slight 2=moderate 3=severe	0=no involvement 1=>0-<10% 2=10-<30%

	4=very severe	4=very severe	4=very severe	3=30-<50% 4=50-<70% 5=70-<90% 6=90-100%
Trunk (T)‡	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 CRF

† 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.

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 (EH + IH + DH) AH + 0.2 (EU + IU + DU) AU + 0.3 (ET + IT + DT) AT + 0.4 (EL + IL + DL) AL

The keys for the letters are provided in Table 8-2.

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

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

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

[redacted]

8.3.3 Liver function tests and liver and/or systemic inflammation markers

Hepatic inflammation markers (i.e. ALT, [redacted]) will be assessed as indicated in Table 8-1. The methods for assessment and recording are specified in the laboratory manual.

Some of the liver function tests will be completed as part of the blood chemistry panel (see Section 8.4.4).

[redacted]

8.3.7 Appropriateness of efficacy assessments

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

[redacted]

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed. For details on AE collection and reporting, refer to Section 10.

8.4.1 Anthropometric assessments

Height, body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes), and waist and hip circumference in centimeters (cm), will be measured as indicated in Table 8-1.

For the assessment of the waist and hip circumference, the patient should be standing upright during the measurements, with arms relaxed at the side, feet evenly spread apart and body weight evenly distributed.

The waist circumference should be measured on bare skin at the end of several consecutive natural breaths, at a level parallel to the floor, midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid axillary line. The hip circumference should be measured on bare skin at a level parallel to the floor, at the largest circumference of the buttocks. For both measurements it is advised to use a stretch-resistant tape that is wrapped snugly around the patient, but not to the point that the tape is constricting (World

Health Organization Dec 2008). It is recommended that waist and hip circumference measurements are performed by the same person throughout the study.

Waist-to-hip ratio (WHR) will be calculated using the following formula:

- WHR = Waist circumference (cm) / Hip circumference (cm)

Body mass index (BMI) will be calculated using the following formula:

- BMI = Body weight (kg)/[height (m^2)]

8.4.2 Physical examination

Physical examinations will be performed as indicated in Table 8-1.

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. In particular, the examination will include recognition of enthesitis, dactylitis, and the patterns of joint, or nail involvement.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an AE must be recorded as an AE.

8.4.3 Vital signs

Vital signs will be measured as indicated in Table 8-1. Vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse measurements. After the patient has been sitting for 5 minutes, with back supported and both feet placed on the floor, SBP and DBP will be measured 3 times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 to 2 minute intervals and the mean of the 3 measurements will be used. The results of all measurements, including the mean measurement, should be recorded in the source data. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

If possible, assessments should be performed by the same study site staff member throughout the study.

Normal blood pressure will be defined as SBP of 90 to < 120 mmHg, and diastolic blood pressure of 60 to < 80 mmHg under the measurement conditions outlined above. Notable blood pressure findings will be hypertension (SBP of ≥ 140 mmHg and/or DBP of ≥ 90 mmHg) or hypotension (SBP of < 90 mmHg and/or a DBP of < 60 mmHg). A blood pressure indicative of prehypertension (SBP of 120 to < 140 mmHg and/or DBP of 80 to < 90 mmHg) will not be regarded as notable (Whelton et al 2017).

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

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

8.4.4 Laboratory evaluations

Laboratory evaluations will be performed as indicated in Table 8-1. A central laboratory will be used for the analysis of all specimens collected except for urine dipstick and pregnancy tests, which will be analysed locally. Details on the collection, shipment of samples and reporting of results by the central laboratory will be provided to Investigators in the laboratory manual. Clinically notable laboratory findings are defined in Appendix 1.

Table 8-4 Laboratory assessments

Test category	Test name
Hematology	Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), Platelets*, Red Blood Cells (RBCs), White Blood Cells (WBCs), , Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Chemistry	Albumin*, Alkaline Phosphatase, Alanine Amino Transferase (ALT*) [redacted] Lactate Dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine Kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin*, Total Cholesterol*, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Total Protein, Triglycerides*, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glycated Hemoglobin (HbA1c), Glucose (fasting)*
[redacted]	
Urinalysis	The central laboratory will provide dipsticks to the sites for local analysis of urine. Dipstick analysis will measure specific gravity, protein, glucose and blood. Microscopy and white blood cell count and red blood cell count sediments will be assessed in case of an abnormal dipstick test. Only samples with abnormal dipstick will be assessed by the central laboratory and the results provided in loaded data and reported to the investigator. Study sites should record the results in the source documentation
Coagulation	International normalized ratio (INR)
Pregnancy test	A serum β-hCG test will be performed for all pre-menopausal women at Screening Visit 1. Any woman with a confirmed positive pregnancy test (hCG > 5 mIU/mL) during Screening will not be eligible for randomization. Urine pregnancy tests will be performed thereafter as shown in Table 8-1. Women of childbearing potential should use an effective method of contraception while on treatment, or longer if required by locally-approved prescribing information (e.g. 20 weeks after the last dose in the European Union and countries where applicable for secukinumab.
Fertility test	A follicle stimulating hormone (FSH) test will be performed if required for fertility testing in the absence of other records of fertility (see Section 8.4.5)

* These parameters will be used as part of the study efficacy analyses described in Section 8.3.3 and

Test category	Test name

Section 8.3.4.

8.4.5 Pregnancy and assessments of fertility

Pregnancy testing

Secukinumab must not be given to pregnant women; therefore, effective methods of birth control must be used for women of childbearing potential (see Exclusion Criteria definitions, Section 5.2).

A serum β-hCG test will be performed in all women of child-bearing potential at Screening. All pre-menopausal women who are not surgically sterile at Screening will have local urine pregnancy tests as indicated in Table 8-1. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued from the trial. Additional pregnancy testing might be performed if requested per local requirements. Refer to Section 10.1.4 for details on reporting of pregnancy. Pregnancy test results are kept in the eCRF.

Assessments of fertility

Refer to Section 5.2 for criteria to determine women that are not of childbearing potential.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of childbearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, follicle stimulating hormone (FSH) testing is required of any female patient who states that they are of non-childbearing potential regardless of reported reproductive/menopausal status at Screening/Baseline.

8.4.6 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Alcohol use disorders identification test (AUDIT)

Any history of alcohol use will be recorded in the CRF. Further, the Alcohol Use Disorders Identification Test (AUDIT) will be performed at Screening Visit 1 and as indicated in Table 8-1. For this purpose, the patients will be interviewed by the site staff. At Screening Visit 1, a 10-item questionnaire will be used, whereas at the following visits, the shortened version (AUDIT-C), a 3-item questionnaire will be used.

8.5.2 Patient reported outcomes

The impact of psoriasis on various aspects of patients' health will be assessed by the following measures:

- Dermatology life quality index
- [redacted]

These QoL assessments should be completed by the patient (in the language he/she is most familiar with) at the scheduled visit before the patient sees the Investigator (or designee) for clinical assessments. The patient should be given sufficient space and time to complete the questionnaires. The study coordinator should check the questionnaires for completeness and encourage the respondent to complete any missing responses. Prior to clinical examination, the Investigator should review the completed questionnaires for responses that may indicate potential AEs or SAEs.

If AEs or SAEs are confirmed, the Investigator must record the events as per the instructions Section 10 of the protocol. The Investigator should not encourage the patient to change the responses reported in the completed questionnaires.

8.5.2.1 Dermatology life quality index

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

This measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 32 different skin conditions and is available in 85 languages. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology.

The recall period is the last week, and the instrument requires 1 to 2 minutes for completion.

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

The DLQI questionnaire will be completed by the patient as indicated in Table 8-1.

[redacted]

[redacted]

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment 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 for a given patient if he/she believes that continuation would negatively impact the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Withdrawal of informed consent
- Emergence of the following AEs:

- Any severe or SAE that is not compatible with administration of study medication, including AEs that require treatment with an unacceptable concomitant medication.
- Onset of lymphoproliferative disease or any malignancy, except for treated basal cell carcinoma, treated actinic keratoses, treated in situ carcinoma of the cervix or non-invasive malignant colon polyps which are being or have been removed.
- Life-threatening infection.
- Severe hypersensitivity reaction or anaphylactic reaction.
- Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the patient at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in Appendix 1).
- Pregnancy.
- Use of any biologic immunomodulating agent except secukinumab.
- Any protocol deviation that results in a significant risk to the patient's safety.
- Disease worsening unacceptable at the Investigator's discretion
- Use of prohibited treatment as per recommendations in the prohibited treatment section.

If discontinuation of study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the patient's premature discontinuation of study treatment and record this information.

If study treatment discontinuation occurs because of study treatment unblinding, please refer to Section 6.2.2.

Discontinuation of study treatment does not require the patient to be discontinued from the study and all ongoing visit assessments except in case of withdrawal of informed consent (see Section 9.1.2). Refer to Section 8 for the visit schedule and assessments.

Patients who prematurely discontinue the study treatment (s.c. secukinumab or placebo) are encouraged to remain in the study to continue the study-related assessments until completion of the study.

Patients who prematurely discontinue completely from the study for any reason should return for the final visit to undergo the EOT assessments (4 weeks after the last study treatment administration of secukinumab). This will be EOT1 (Week 12) for patients who prematurely discontinue during Treatment Period 1 and EOT2 (Week 24) for patients who prematurely discontinue during Treatment Period 2.

If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/ pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

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

- New/concomitant treatments.
- Adverse events/SAEs.

9.1.2 Withdrawal of informed consent

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

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

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the 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.

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

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

9.1.3 Lost to follow-up

For patients 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 patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time. Reasons for early termination may include:

- Unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, patients 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 or Novartis depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last patient finishes their Final Visit (Week 24/Early Withdrawal) and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision (e.g. each patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

All randomized and/or treated patients should have a safety follow-up conducted 30 days after the last administration of study treatment. This will be performed at Week 24 for patients who complete the study (last administration received at Week 20). The information collected is kept as source documentation. All SAEs reported during this period must be reported as described in Section 10.1.3. Attempts to contact the patient should be recorded in the source documentation.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The Investigator has the responsibility for managing the safety of individual patient and identifying AEs.

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

The occurrence of AEs 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.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade:
    - Mild: usually transient in nature and generally not interfering with normal activities.
    - Moderate: sufficiently discomforting to interfere with normal activities.

- Severe: prevents normal activities.

2. Its relationship to the study treatment (suspected: yes or no). If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be "not suspected." The rationale for this guidance is that the symptoms of lack of efficacy or progression of underlying illness are not caused by the study treatment, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient.
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding the study treatment.

   All AEs must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed.
   - Dose reduced/increased.
   - Drug interrupted/withdrawn.
6. Its outcome.

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

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

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

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

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

Clinically significant abnormal laboratory values or test results 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 patients

with the underlying disease. Clinically notable laboratory values and vital signs are presented in Appendix 1.

10.1.2 Serious adverse events

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

- Fatal
- Life-threatening

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 the ICH-E2D Guidelines).

- Results in persistent or significant disability/incapacity.
- Constitutes a congenital anomaly/birth defect.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition.
  - 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.
- Is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

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. Such events should be considered as "medically significant". 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 the ICH-E2D Guidelines).

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

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

All reports of intentional misuse and abuse of the product are also considered SAEs irrespective if a clinical event has occurred (Section 10.1.5).

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site.

Serious adverse events occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis.

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.

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 CMO&PS 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.

Any SAEs experienced after the 30-day period following the last administration of study treatment should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment.

10.1.4 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 should be recorded on a Clinical Trial Pregnancy Form and reported by the Investigator/qualified study center staff to the Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother ((please confirm)).

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, 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 recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness (Table 10-1).

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

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

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

10.2 Additional safety monitoring

10.2.1 Liver safety monitoring

There has been no safety signal for liver toxicity with secukinumab to date in approximately 13000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17a on the liver. Standard liver function tests will be obtained at regular intervals, but special measures for liver safety monitoring are not planned over and above those collected for the study endpoints (see Section 8.3.3, Section 8.3.4 and Section 8.4.4). For further information on standard liver function tests, see Appendix 1.

10.2.2 Renal safety monitoring

There has been no safety signal for nephrotoxicity with secukinumab to date in approximately 13000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17a on the kidney. All patients with laboratory tests containing clinically significant abnormal values (see Appendix 1 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function tests (BUN, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

10.2.3 Steering committee

The Steering Committee will be established comprising investigators participating in the trial, i.e. not being Novartis/sponsor representatives from the Clinical Trial Team.

The Steering Committee will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The Steering Committee will review protocol amendments as appropriate. Together with the clinical trial team, the Steering Committee will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in the steering committee charter.

11 Data collection and database management

11.1 Data collection

Designated Investigator staff will enter the data required by the protocol into electronic case report forms (eCRFs). The eCRFs will be built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the Investigator will receive copies of the patient data for archiving at the investigational site.

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

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO. Additionally, a central analytics organization may analyze data and identify risks and 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, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The Investigator must also keep the original ICF signed by the patient (a signed copy is given to the patient).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the 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 will be disclosed.

12 Data analysis and statistical methods

The data will be analyzed by Novartis and/or a designated CRO.

The analyses will be conducted on all patient data after database lock for the study. Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The following analysis sets will be used in this study:

Randomized Analysis Set (RAS): The RAS is defined as all patients who were randomized. Unless otherwise specified, miss-randomized patients will be excluded from the RAS.

Full Analysis Set (FAS): The FAS comprises all patients to whom study treatment/reference treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Safety Set: The Safety Set includes all patients who received at least one dose of study treatment/reference treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

12.2 Subject demographics and other baseline characteristics

Demographic and other Baseline data including disease characteristics will be listed and summarized descriptively by treatment group and in total for the FAS and Safety Set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at Baseline will be summarized by system organ class and preferred term (PT), and by treatment group.

12.3 Treatments

The Safety Set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The duration of exposure to study treatment by treatment group will be summarized by means of descriptive statistics using the Safety Set. In addition, the number of patients with exposure of certain thresholds will be displayed. Compliance will be calculated based on documented study drug administrations and syringe counts and displayed by treatment group and study phase.

Concomitant medications and significant non-drug therapies received prior to and after the start of the study treatment will be listed and summarized according to the anatomical therapeutic chemical (ATC) classification system, by treatment group. Prior treatments are defined as treatments taken and stopped prior to first dose of study treatment. Any treatment given at least once between the day of first dose of randomized study treatment and the last day of study visit will be a concomitant treatment, including those which were started pre-Baseline and continued into the treatment period. Treatments will be presented in alphabetical order, by ATC codes and grouped by anatomical main group. Tables will also show the overall number and percentage of patients receiving at least one treatment of a particular ATC.

12.4 Analysis of the primary endpoint

12.4.1 Definition of primary endpoint

The primary aim of this study will be to demonstrate the superiority of secukinumab compared to placebo in patients with moderate to severe chronic plaque-type psoriasis and NAFLD with respect to PASI90 response at Week 12.

The primary endpoint variable is the PASI90 response at Week 12.

The analysis of the primary variable will be based on the following estimand:

- Analysis set: FAS
- Variable of interest: PASI 90 response at Week 12
- Intercurrent event: study discontinuation – effect between secukinumab versus placebo in patients with moderate to severe chronic plaque-type psoriasis and NAFLD irrespective of adherence to treatment. Patients who discontinue the trial prematurely will be counted as non-responders.
- Summary measure: Odds ratio (OR)

12.4.2 Statistical model, hypothesis, and method of analysis

The null hypothesis to be rejected is that the OR of a PASI90 response for patients with secukinumab vs. patients with placebo are ≥ 1 after 12 weeks.

Let pj denote the probability of a PASI90 response at 12 weeks for treatment group j, j=0,1 where

- 0 corresponds to placebo
- 1 corresponds to secukinumab 300 mg

The following hypotheses will be tested:

H_0: $(p_0 / 1\text{-}p_0)) / (p_1 / 1\text{-}p_1)) \geq 1$ versus H_A: $(p_0 / 1\text{-}p_0)) / (p_1 / 1\text{-}p_1)) < 1$

The primary analysis will be performed comparing treatments with respect to the primary efficacy variable in a logistic regression model with the factors treatment group and center as factors and PASI score at Baseline (Day 1) as covariates. The OR and its 95% confidence interval (CI) and p-value will be given. The primary analysis will be based on the FAS and will be performed when all patients have completed the Week 12 assessment.

12.4.3 Handling of missing values/censoring/discontinuations

For the analysis of the primary endpoint PASI90 response at Week 12, all patients of the FAS will be included. A patient with a missing assessment will be considered as a non-responder. Missing values of secondary endpoints or other outcomes (e.g. quality of life, safety or laboratory measurements) will not be replaced.

12.4.4 Sensitivity and supportive analyses

A “while on treatment” estimand will be calculated as a sensitivity analysis. It will be based on the following estimand:

- Analysis set: FAS
- Variable of interest: PASI 90 response at Week 12
- Intercurrent event: study discontinuation – effect between secukinumab versus placebo in patients with moderate to severe chronic plaque-type psoriasis and NAFLD. A patient with a missing assessment will be considered as a responder if he/she has met the response criterion already at the time of drop out. Otherwise, he/she will be considered as a non-responder. Summary measure: OR.

12.5 Analysis of secondary endpoints

Serum ALT level at Week 12

The analysis of historic data from non-NAFLD patients suggests that the distribution of ALT values might be highly skewed to the left; however, after a log-transformation the distribution appeared quite symmetric, bell-shaped and could be well approximated by a normal distribution. Therefore, the log-transformed ALT-values will be used for the analysis.

For this secondary objective, this study is meant as a Proof-of-Concept study, i.e. to evaluate if there is any evidence for a beneficial effect on this endpoint and to provide the basis for the planning of further, confirmatory studies; therefore a Bayesian methodology seems adequate for the analyses of possible drug effects on ALT.

A sample from the posterior distribution of the difference between treatments of the log(ALT) levels will be produced using the BAYES-option is SAS PROC GENMOD (with the default, non-informative prior). These posterior samples will be re-transformed (exponentiated) and the percentage of samples < 1, $< .9$, $<.8$ and $<.7$ (corresponding to the posterior probabilities of any reduction resp. reductions of at least 10%, 20% or 30% of ALT levels under secukinumab compared to placebo) will be calculated. The study will suggest to continue the development of secukinumab for hepatic inflammation, if the posterior probability of any effect (significance) is at least 90% and if the posterior probability of a relevant effect ($> 20\%$ reduction) is at least 50%.

DLQI at Week 12

The DLQI measures functional disability of adult patients with dermatological disorders and had been utilized as a relevant clinical measure in a range of dermatology clinical trials. The DLQI is a simple, validated, self-administered 10-item questionnaire. The instrument contains 6 functional scales (i.e. symptoms and feeling, daily activities, leisure, work and school, personal relationships, treatment).

Each question is answered with the following response: “not at all,” “a little,” “a lot,” or “very much”. Seven scores will be derived from the DLQI: the total score of each of the six dimensions as well as the total score over all items. The higher the score, the more quality of life is impaired.

For total DLQI as well as for each of its 7 sub-dimensions the percentage change from baseline will be derived. Descriptive summary statistics will be provided for absolute values as well as for the percentage change by visit and treatment group. Additionally, the percentage of patients achieving a DLQI-score of 0 or 1 (DLQI 0/1) will be tabulated.

12.5.1 Safety endpoints

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) will include only data from the on-treatment period with the exception of Baseline data, which will also be summarized where appropriate (e.g. change from Baseline summaries). In addition, a separate summary for deaths including on-treatment and post-treatment deaths will be provided. In particular, summary tables for AEs will

summarize only on-treatment events, with a start date during the on-treatment period (i.e. treatment-emergent AEs as defined below).

Adverse events

All information obtained on AEs will be displayed by treatment group and patient.

The number (and percentage) of patients with treatment-emergent AEs will be summarized in the following ways:

- By treatment group, primary SOC and PT.
- By treatment group, primary SOC, PT and maximum severity.

Separate summaries will be provided for study medication related AEs, death, serious AEs, other significant AEs leading to discontinuation.

A patient with multiple AEs within a primary SOC is only counted once towards the total of the primary SOC.

Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time, and if ranges are available, abnormalities will be flagged. 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.

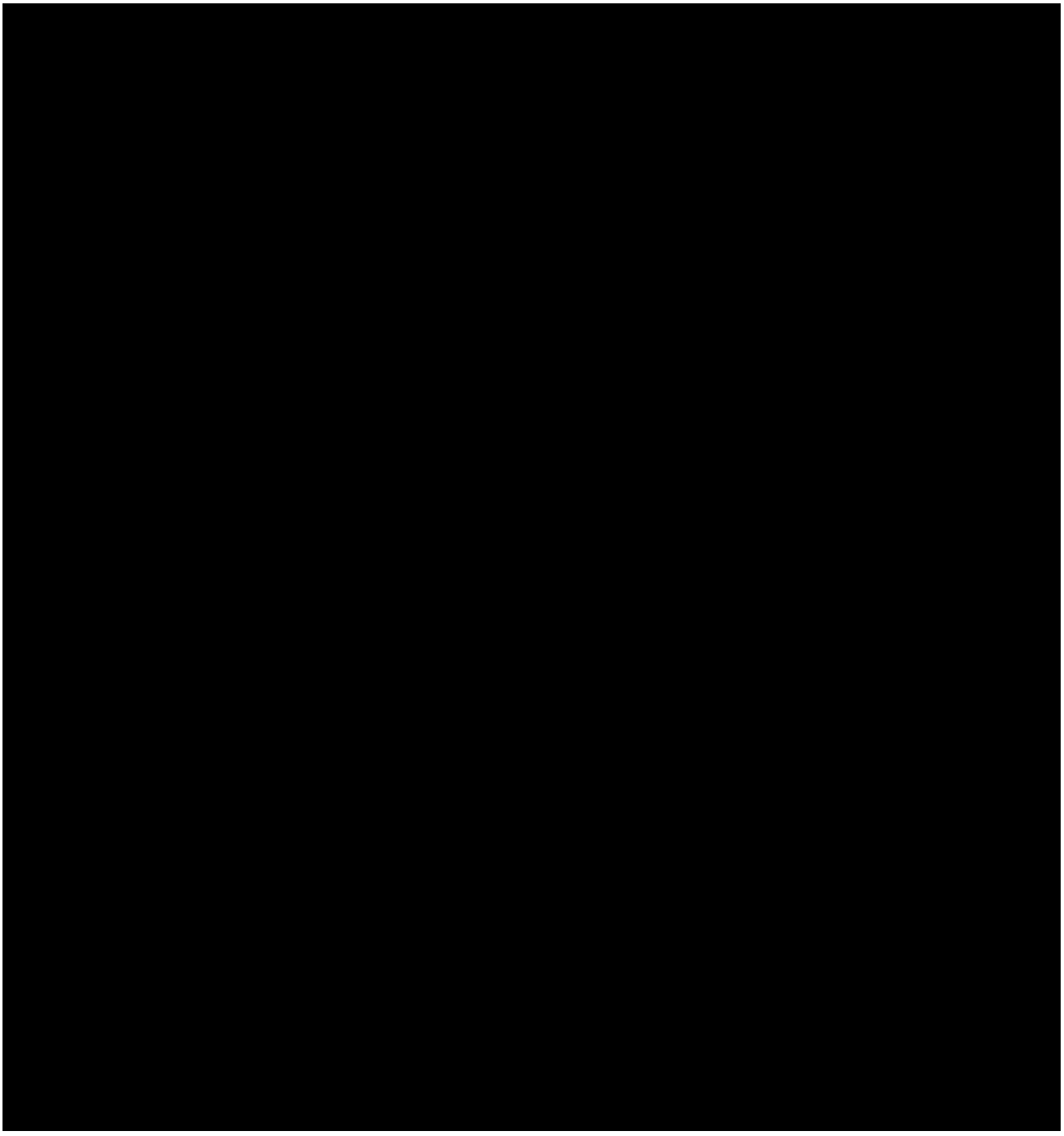
Clinical laboratory evaluations

All laboratory data will be listed by treatment group, patient, and visit and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit. Change from baseline will only be summarized for patients with both Baseline and post-baseline values. Baseline to the worst on-treatment value.

12.7 Interim analyses

No interim analysis will be performed. However, the final analysis of the data of Treatment Period 1 (including the primary endpoint) may already be conducted before all patients have

finished Treatment Period 2. Details about access to these data and about the maintenance of the blind while Treatment Period 2 is still ongoing will be specified in a separate document.



13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the Investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

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

13.4 Quality control and quality assurance

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

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

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

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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

14.1 Protocol amendments

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

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values

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 8.4.3.

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

Liver function and related variables

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

Renal function and electrolyte variables

Creatinine (serum):	> 1.5 x ULN

Hematology variables

Hemoglobin:	≥ 20 g/dL decrease from Baseline
Platelet count:	< lower limit of normal (LLN)
White blood cell count:	< 0.8 x LLN
Neutrophils:	< 0.9 x LLN
Eosinophils:	> 1.1 x ULN
Lymphocytes:	> 1.1 x ULN

Urinalysis variable

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

16.2 Appendix 2: The American Heart Association (AHA) Recommended Diet

Optimization of diet can result in a marked triglyceride-lowering effect that ranges between 20% and 50%. Good practices include weight loss, reducing simple carbohydrates at the expense of increasing dietary fiber, eliminating industrial-produced trans fatty acids, restricting fructose and saturated fatty acids, implementing a Mediterranean-style diet, and consuming marine-derived omega-3 PUFA.

AHA recommends the following:

Eat a variety of fruit and vegetable servings every day. Dark green, deep orange, or yellow fruits and vegetables are especially nutritious. Examples include spinach, carrots, peaches, and berries. Eat a variety of grain products every day. Include whole-grain foods that have lots of fiber and nutrients. Examples of whole grains include oats, whole wheat bread, and brown rice. Eat fish at least 2 times each week. Oily fish, which contain omega-3 fatty acids, are best for your heart. These fish include tuna, salmon, mackerel, lake trout, herring, and sardines. Stay at a healthy weight by balancing the amount of calories you eat with the activity you do every day. If you want to lose weight, increase your activity level to burn more calories than you eat.

Eat foods low in saturated fat and cholesterol. Try to choose the following foods:

- Lean meats and meat alternatives like beans or tofu
- Fish, vegetables, beans, and nuts
- Nonfat and low-fat dairy products
- Polyunsaturated or monounsaturated fats, like canola and olive oils, to replace saturated fats, such as butter

Read food labels and limit the amount of Trans fat you eat. Trans fat is found in many processed foods made with shortening or with partially hydrogenated or hydrogenated vegetable oils. These foods include cookies, crackers, chips, and many snack foods.

Limit sodium intake to less than 2,300 mg of sodium a day (about one teaspoon). Choose and prepare foods with little or no salt.

Limit alcohol intake to 2 drinks a day for men and 1 drink a day for women.

Limit drinks and foods with added sugar.

16.3 Appendix 3: 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 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

Criteria	Event type	Actions required	Follow-up monitoring
≤ 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.