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AIN457/Secukinumab

Clinical Trial Protocol CAIN457FDE04 / NCT04632927

A 28-week, randomized, double-blind, active-controlled, multicenter study to evaluate the efficacy of subcutaneously administered secukinumab compared to ustekinumab in adult patients with psoriatic arthritis and failure of TNFα-inhibitor treatment (AgAIN)

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Amendment 1 (10-SEP-2024)

Amendment rationale

As of 31 Jan 2024, all screening/recruitment activities of this study were stopped due to severe recruitment issues, since 36 months after start of screening only 37% (116 of 310 patients) were recruited although extensive measures to enhance recruitment were taken. Therefore, Amendment 1 is being implemented.

The study is currently ongoing and in total 119 participants have been randomized. Under the previous assumptions for the sample size the power will be ~55%. Hence, only a descriptive analysis will be performed for all primary and secondary endpoints [redacted] have been removed.

Furthermore, the Hy's law language section was adapted to ensure compliance with FDA request for expedited reporting of potential Hy's Law cases.

Changes to protocol:

Section	Changes made
Protocol Summary	Update of [redacted] Data Analysis Section
[redacted]	[redacted]
[redacted]	[redacted]
Section 10.1.1 Adverse Events	Update of AE safety follow-up to align with SAE safety follow-up
Section 10.1.3 SAE reporting	Inclusion of Hy's law language
Section 10.1.5 Reporting of study treatment errors including misuse/abuse	Updated based on current requirements
Section 12.4.2 Statistical model, hypothesis, and method of analysis & Section 12.8. Sample size calculation	Updated to reflect that analysis will only be descriptive
[redacted]	[redacted]
[redacted]	[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-Drug Antibodies
AE	Adverse Event
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
anti-CCP	Anti-Cyclic Citrullinated Peptide
anti-dsDNA	Anti-Double Stranded DNA Antibodies
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chronical
BSA	Body Surface Area
BSL	Baseline
CASPAR	Classification Criteria for Psoriatic Arthritis
CD	Cluster of Differentiation
cDMARD	Conventional Disease Modifying Anti-Rheumatic Drugs (also known as non-biologic DMARDs)
CFR	Code of Federal Regulations (U.S.)
cm	Centimeter
COX	Cyclooxygenase
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
[redacted]	[redacted]
[redacted]	[redacted]
DAS	Disease Activity Score
dL	Deciliter
DLQI	Dermatology Life Quality Index
DMARD(s)	Disease-Modifying Antirheumatic Drug(s)
DSM	Drug Supply Management
DSUR	Developmental Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EMA/EMEA	European Medicines Agency
EOS	End of Study
[redacted]	[redacted]
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EULAR	European League Against Rheumatism
F/FUP	Follow-Up
FACIT-Fatigue©	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
G	Gram

GCP	Good Clinical Practice
HAQ-DI©	Health Assessment Questionnaire – Disability Index
hCG	Human Chorionic Gonadotropin
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	Immunoglobuline
[redacted]	[redacted]
IL	Interleukin
IN	Investigator Notification
IR	Inadequate Responder
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine System
JAK	Janus Kinase
kg	Kilogram
LDI	Leeds Dactylitis Index
LDL	Low Density Lipoprotein
LEI	Leeds Enthesitis Index
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MACE	Major Adverse Cardiovascular Events
MAR	Missing at Random
[redacted]	[redacted]
MCS	Mental Component Summary
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Multiple Imputation
mL	Milliliter
mm	Millimeter
MMRM	Mixed-effect Model for Repeated Measures
[redacted]	[redacted]
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
[redacted]	[redacted]

NSAID	Non-Steroidal Anti-Inflammatory Drug
[redacted]	[redacted]
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PFS	Prefilled Syringe
[redacted]	[redacted]
PRN	*Pro re nata* / As Required
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
PsAQoL	Psoriatic Arthritis Quality of Life
[redacted]	[redacted]
PUVA	Psoralen Ultraviolet Light A
QMS	Quality Management System
QoL	Quality of Life
QTcF	Fridericia QT Correction Formula
R	Randomization
RAS	Randomized Analysis Set
RBC	Red Blood Cell
RF	Rheumatoid Factor
SAE	Serious Adverse Event
s.c.	Subcutaneous(ly)
[redacted]	[redacted]
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SJC	Swollen Joint Count
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOP	Standard Operating Procedures
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reactions
SV	Screening Visit
TB	Tuberculosis
Th	T helper
t.i.d.	Three Times Daily
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor
TNFα	Tumor Necrosis Factor Alpha
tsDMARD	Targeted Synthetic Disease Modifying Anti-Rheumatic Drug
ULN	Upper Limit of Normal
UV	Ultraviolet
UVA	Ultraviolet Light A
UVB	Ultraviolet Light B
V	Visit
VAS	Visual Analog Scale

WBC	White Blood Cell
WHO	World Health Organization
[redacted]	[redacted]

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
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
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
DMARDs	Disease modifying anti-rheumatic drugs. This drug class includes biological DMARDs (bDMARDs), conventional (systemic) DMARDs (cDMARDs, csDMARDs) and targeted systemic DMARDs (tsDMARDs).
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic data capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
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)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease
Patient	An individual with the condition of interest for the study
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 ID/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

Protocol summary

Protocol number	CAIN457FDE04
Full Title	A 28-week, randomized, double-blind, active controlled, multicenter study to evaluate the efficacy of subcutaneously administered secukinumab compared to ustekinumab in adult patients with psoriatic arthritis and failure of TNFα-inhibitor treatment (AgAIN)
Brief title	Efficacy of secukinumab compared to ustekinumab in adults with active psoriatic arthritis and failure of TNFα-inhibitor treatment
Sponsor and Clinical Phase	Novartis, Phase IIIb
Investigation type	Biological
Study type	Interventional
Purpose and rationale	Secukinumab has already been shown to be superior to ustekinumab in the treatment of moderate-to-severe skin psoriasis. To date, no results are available for psoriatic arthritis (PsA) in this setting. Additionally, data regarding the tumor necrosis factor α inadequate responder (TNFα-IR) population using the aforementioned treatment in a dedicated clinical trial are lacking. This head-to-head study will close this gap and generate valuable insights into the mechanistic process after anti-TNFα failure. In addition, secukinumab and ustekinumab were just recently listed as appropriate comparators within the German Health Technology Assessment (HTA) process for the subpopulation of PsA patients who failed biologics treatment. The overall study design is intended to reflect efficacy insights, prescription information, treatment guidelines and clinical practice in the targeted patient population, thereby supporting future HTAs of secukinumab in Germany.
Primary objective	• To demonstrate that secukinumab 300 mg s.c. is superior to ustekinumab 45/90 mg s.c. at week 28 based on the proportion of patients achieving an improvement in health assessment questionnaire-disability index (HAQ-DI©) score ≥ 0.35 versus Baseline.
Secondary objectives	To demonstrate • The efficacy of secukinumab 300 mg s.c. is higher to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving a psoriasis area and severity index (PASI) 90 response. • Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement of ≥ 10 mm for the patient's assessment of pain (visual analog scale, VAS). • The mean change from Baseline on secukinumab 300 mg s.c. is higher to ustekinumab 45/90 mg s.c. at week 28 for the tender joint count (TJC) 68. • The mean change from Baseline on secukinumab 300 mg s.c. is higher to ustekinumab 45/90 mg s.c. at week 28 for the swollen joint count (SJC) 66. • Efficacy of secukinumab 300 mg s.c. is higher to ustekinumab 45/90 mg s.c. at week 28 based regarding the proportion of patients achieving a PASI 100 response. • Efficacy of secukinumab 300 mg s.c. is higher to ustekinumab 45/90 mg s.c. at week 28 based on the proportion of patients achieving a PASI 75 response.

	• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement of 10 mm on patient's global assessment of disease activity (VAS). • Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement of 10 mm on patient's global assessment of psoriasis and arthritis disease activity (VAS). • Efficacy of secukinumab 300 mg s.c. is higher to ustekinumab 45/90 mg s.c. at week 28 based on the proportion of patients achieving minimal disease activity (MDA). • The mean change from Baseline on secukinumab 300 mg s.c. is higher to ustekinumab 45/90 mg s.c. at week 28 for the Leeds enthesitis index (LEI). • The mean change from Baseline on secukinumab 300 mg s.c. is higher to ustekinumab 45/90 mg s.c. at week 28 for the Leeds dactylitis index (LDI). • The mean change from baseline on secukinumab 300 mg s.c. is higher to ustekinumab 45/90 mg s.c. at week 28 for Psoriatic Arthritis Quality of Life (PsAQoL). • The efficacy of secukinumab 300 mg s.c. is higher to ustekinumab 45/90 mg s.c. at week 28 based on the proportion of patients achieving an improvement of ≥ 4 points for Functional Assessment of Chronic Illness Therapy – fatigue (FACIT-Fatigue©). • The efficacy of secukinumab 300 mg s.c. is higher to ustekinumab 45/90 mg s.c. at week 28 based on the proportion of patients achieving a Dermatology Life Quality Index (DLQI) 0/1 response. • To evaluate the safety and tolerability of secukinumab 300 mg s.c. compared with ustekinumab 45/90 mg s.c. as assessed by vital signs, clinical laboratory values, and AE monitoring.
Study design	This randomized, double-blind, active-controlled, multicenter, study will assess the superiority of secukinumab to ustekinumab for treating patients with active PsA who failed TNFα-inhibitor treatment. The study will include a screening period of up to 10 weeks, a treatment period of 28 weeks, and a follow-up period of 8 weeks.
Population	The study population will consist of 310 patients fulfilling Classification criteria for Psoriatic Arthritis (CASPAR) and have shown previous inadequate response to TNFα-inhibitors.
Inclusion criteria	1. Informed consent must be obtained before any assessment is performed. 2. Male or non-pregnant, non-lactating female subjects at least 18 years of age. 3. Diagnosis of PsA as classified by CASPAR criteria for at least 6 months before randomization. 4. Active PsA at Baseline defined as ≥3 tender joints out of 68 and ≥3 swollen joints out of 66 (dactylitis of a digit counts as one joint each). 5. Inadequate response or intolerance to previous or current treatment with at least one TNFα-inhibitor administered at an approved dose for the given duration according to the respective Summary of Product Characteristics (SmPC). 6. Inadequate response or intolerance to conventional disease modifying anti-rheumatic drugs (cDMARDs) and to at least one TNFα-inhibitor

	must have been documented in the patient's medical history or reported by the patient or determined by the investigator at Screening. 7. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies negative at screening. 8. Diagnosis of active plaque psoriasis, with at least one psoriatic plaque or nail changes consistent with psoriasis or documented history of plaque psoriasis. 9. Patients taking methotrexate (MTX) (≤ 30 mg/week) are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization and should remain on a stable dose up to Week 28. 10. Patients on MTX must be on folic acid supplementation at randomization. 11. Patients who are on a disease modifying anti-rheumatic drug (DMARD) other than MTX must discontinue the DMARD 4 weeks prior to randomization visit except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine wash-out has been performed. 12. Patients who are regularly receiving non-steroidal anti-inflammatory drugs (NSAIDs) as part of their PsA therapy are required to be on a stable dose for at least 2 weeks before study randomization and should not increase the dose up to Week 28. 13. Patients receiving corticosteroids must be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 28.
Exclusion criteria	1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test. 2. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and minimum 16 weeks or longer if local label requires it after the last dose (e.g. 20 weeks for secukinumab, 15 weeks for ustekinumab in the European Union (EU)). Effective contraception methods include: a. 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. b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment. c. 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. d. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps). e. Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms

	of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking the investigational drug. In case local regulations deviate from the methods listed, local regulations apply and will be described in the informed consent form (ICF). Women are considered post-menopausal and not of child-bearing potential if they have had at least 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 child-bearing potential. 3. Previous exposure to secukinumab, ustekinumab or any other biologic drug directly targeting IL-17, IL-17 receptor, IL-12 or IL-23. 4. Patients for whom the use of secukinumab or ustekinumab is contraindicated. 5. Use of any other investigational drug within 4 weeks or within a period of 5 half-lives of the investigational treatment prior to the Baseline Visit, whichever is longer, until the expected pharmacodynamic effect has vanished. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g., alemtuzumab (Campath®), anti-CD4, anti-CD5, anti-CD3, and anti-CD19). 6. Chest X-ray or chest magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process obtained within 3 months prior to Screening and evaluated by a qualified physician. 7. Patients receiving high potency opioid analgesics including but not limited to methadone, hydromorphone, and morphine. 8. Ongoing use of prohibited psoriasis treatments/medications (e.g., topical corticosteroids or ultraviolet therapy at randomization). The following wash out periods need to be observed: a. Oral or topical retinoids: 4 weeks b. Photochemotherapy (e.g. PUVA): 4 weeks c. Phototherapy (UVA or UVB): 2 weeks d. Topical skin treatment (except in face, eyes, scalp and genital area during screening; only corticosteroids with mild to moderate potency): 2 weeks. 9. History of hypersensitivity to any of the study drugs or excipients or to drugs of similar chemical classes. 10. Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization. 11. Any therapy by intra-articular injections (e.g., corticosteroid) within 4 weeks before randomization. 12. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy.

	13. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the subject and/or places the subject at unacceptable risk for participation in an immunomodulatory therapy. 14. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV) and uncontrolled diabetes. 15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFTs) such as aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase / serum glutamic pyruvic transaminase (ALT/SGPT), alkaline phosphatase or serum bilirubin. The investigator should be guided by the following criteria: a. Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible and in all cases, at least prior to enrollment/randomization, to rule out any possible lab error. b. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. 16. History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a serum creatinine level exceeding 1.8 mg/dL (159.12 µmol/L). 17. Screening total white blood cell (WBC) count <3,000/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL (85 g/L). 18. Active systemic infections during the last two weeks (exception: common cold) prior to randomization. 19. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis (TB) infection as defined by a positive QuantiFERON TB-Plus test. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active TB. If presence of latent TB is established then treatment according to local country guidelines must have been initiated prior to enrollment. 20. Live vaccinations within 6 weeks prior to Baseline or planned vaccination during study participation until 12 weeks after last study treatment administration. 21. Proven infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization. 22. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed). 23. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the subject unsuitable for the trial. 24. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).

	25. 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. 26. Donation or loss of 400 mL or more of blood within 8 weeks before randomization. 27. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization.
Study treatment	• Investigational treatment o Secukinumab 150 mg, 1 ml liquid formulation in a pre-filled syringe (PFS) (2 x 1 ml PFS for 300 mg dose) • Reference treatment o Placebo, 1 mL liquid formulation in a PFS o Ustekinumab 45 mg/0.5 mL or 90 mg/1 mL liquid formulation in a PFS
Efficacy assessments	The main efficacy assessments are as follows: • Health assessment questionnaire-disability index (HAQ-DI©) score • Psoriasis area and severity index (PASI) 90, PASI 100, PASI 75 • Patient's global assessment of pain on VAS • Tender joint count 68 (TJC 68) • Swollen joint count 66 (SJC 66) • Patient's global assessment of disease activity (VAS) • Patient's global assessment of psoriasis and arthritis disease activity (VAS) • Proportion of patients achieving minimal disease activity (MDA) • Leeds enthesitis index (LEI) • Leeds dactylitis index (LDI) [redacted]
Safety assessments	• Evaluation of adverse events (AEs)/serious adverse events (SAEs) • Physical examination • Vital signs • Height and weight • QuantiFERON TB-Plus test • Local tolerability (injection site reactions) • Laboratory evaluations (hematology, clinical chemistry, lipids) • Pregnancy and assessment of fertility • Tolerability of study treatment
Other assessments	• Quality of life (QoL) questionnaires/patient reported outcomes [redacted]
Data analysis	Due to low enrollment, only a descriptive analysis will be performed.

	The primary analysis will be performed comparing treatments with respect to the primary efficacy variable, the proportion of patients achieving a HAQ-DI© score ≥ 0.35 versus Baseline, by means of a logistic regression model with treatment and randomization strata as factors and HAQ-DI© score as covariates. The main measure of effect, the odds ratio, with corresponding 95% confidence interval (CI) and the p-value (both Wald) will be given. The null hypothesis of equal odds will be rejected, if the two-sided p-value from the logistic regression model for the factor treatment is below the significance threshold of 0.05. Sensitivity as well as supportive subgroup analyses will be conducted in order to provide evidence for the robustness of the main results. These analyses will center on the deviations in model assumptions and the treatment of missing values.
Key words	psoriatic arthritis, secukinumab, ustekinumab, monoclonal antibody, CASPAR

1 Introduction

1.1 Background

Psoriatic arthritis (PsA) is an immune-mediated chronic inflammatory disease that can affect peripheral and axial joints, entheses and the skin. Additional common manifestations are nail dystrophy, dactylitis or spine involvement accompanied by comorbidities with impact e.g. on cardiovascular risk. PsA is associated with impaired physical function and poor quality of life (QoL) and thus constitutes a major socioeconomic burden (Gladman 2005, Rosen et al 2012). The majority of patients will have psoriasis prior to the occurrence of the associated arthritis and are typically under treatment for their skin disease.

Pathogenesis-based interventions, particularly therapies targeting tumor necrosis factor alpha (TNFα) show improved outcomes in patients with PsA. Effectiveness and safety have been demonstrated over many years (Ramiro et al 2016). However, despite this progress, approximately 30% of patients fail TNFα inhibitor treatment through inadequate response (IR). They might never achieve a response due to a dominant non-TNFα inflammatory pathway (primary non-responder), show loss of efficacy over time (secondary inefficacy) or have to discontinue treatment because of adverse events (AEs) including intolerance. Switching to a second- or even third-line anti-TNFα therapy ("anti-TNF cycling") may be successful, but most studies show an insufficient response as the same molecular and inflammatory pathways are targeted. The probability of exhibiting a good response within the same treatment class is lower than for the first treatment. As seen not only in rheumatoid arthritis but also in PsA, only a small number of primary non-responsive patients switching to a second anti-TNFα achieve a significant clinical response and the number of patients achieving a sufficient response on the third anti-TNFα is negligible. These patients are in need of further therapeutic options (Gomez-Reino et al 2006, Cantini et al 2017). Real world evidence obtained from national registries and observational studies indicates a discontinuation of first-line TNFα inhibitor treatment ranging between 17.1% and 67.5% (Cantini et al 2017).

Alternative biological treatment options besides TNFα inhibitors include inhibitors for Interleukin (IL)-12/IL-23 (ustekinumab) and IL-17A (secukinumab and ixekizumab).

The IL-17/IL-23 axis plays a central role in the pathogenesis of psoriasis, PsA and axial spondyloarthritis (McGonagle et al 2019). The cytokine IL-17A and its receptor are highly expressed in psoriatic diseases including PsA. IL-17A is one of the main cytokines involved in the inflammatory process in PsA finally leading to destruction, loss of joint function and poor quality of life of affected patients. It is produced by a variety of immune cells during the course of the disease including T helper (Th) 17 cells, γδT cells, macrophages and type 3 innate lymphoid cells (Ivanov et al 2006, Lombes et al 2015). Additionally, IL-23 belongs to the major molecules leading to a damaging course of the disease by inducing differentiation, activation and expansion of Th17 cells which are an effector of the inflammatory process and the main source of IL-17A (Gaffen et al 2014).

Secukinumab, a human monoclonal antibody that inhibits the effector function of IL-17A, has shown better efficacy compared to placebo in several phase III trials for PsA including the FUTURE-study program which involved over 2700 patients. Rapid improvement of key clinical domains of the disease signs and symptoms could be demonstrated not only for anti-

TNFα naive patients but also for patients showing an inadequate response regarding prior anti-TNFα treatment (McInnes et al 2015; Kavanaugh et al 2016).

Just recently secukinumab and ustekinumab have been added to the list of appropriate comparators within the German health technology assessment (HTA) process for the subpopulation of PsA patients who fail TNFα inhibitor treatment. Previously, only TNFα inhibitors were listed as an appropriate comparator.

Within the context of the life cycle management of secukinumab including several planned new indications in the next years this update of the list of appropriate comparators provides – besides important scientific data – an additional opportunity to conduct a study to support the upcoming HTAs.

1.2 Purpose

Secukinumab has already been shown to be superior to ustekinumab in the treatment of moderate-to-severe psoriasis (Blauvelt et al 2017, Bagel et al 2018). To date, no equivalent data are available for the TNFα-IR population in PsA using the aforementioned treatment in a dedicated clinical trial. This 28-week study will close this scientific gap and generate valuable insights into the mechanistic process in PsA patients after failure of TNFα inhibition.

In addition to the scientific aspect, secukinumab and ustekinumab were just recently listed as appropriate comparators – only TNFα inhibitors until now – within the German HTA process for the subpopulation of PsA patients who failed TNFα inhibition. Therefore, this study will evaluate the efficacy and safety of secukinumab compared to ustekinumab in a head-to-head setting. The overall study design is intended to reflect prescription information, treatment guidelines and clinical practice in the targeted patient population, thereby supporting future HTAs.

2 Objectives and endpoints

The study objectives and related endpoints are presented in Table 2-1.

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
• To demonstrate that secukinumab 300 mg s.c. is superior to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement in HAQ-DI© score ≥ 0.35 versus Baseline.	• Proportion of patients achieving a HAQ-DI© response at Week 28.
Secondary objectives	**Endpoints for secondary objectives**
To demonstrate that:	
• The efficacy of secukinumab 300 mg s.c. is higher compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving a PASI 90 response.	• Proportion of patients achieving a PASI 90 response at Week 28.
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement of ≥ 10 mm for the patient's assessment of pain on VAS..	• Proportion of patients achieving an improvement on VAS at Week 28 for patient's assessment of pain.
• The mean change from Baseline on secukinumab 300 mg s.c. is higher compared to ustekinumab 45/90 mg s.c. at Week 28 for the TJC 68.	• Between-treatment difference in change from baseline to Week 28 for the TJC.
• The mean change from Baseline on secukinumab 300 mg s.c. is higher compared to ustekinumab 45/90 mg s.c. at Week 28 for the SJC 66.	• Between-treatment difference in change from baseline to Week 28 for the SJC.
• Secukinumab 300 mg s.c. is shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving a PASI 100 response.	• Proportion of patients achieving a PASI 100 response at Week 28.
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving a PASI 75 response.	• Proportion of patients achieving a PASI 75 response at Week 28.
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement of 10 mm for the patient's global assessment of disease activity (VAS).	• Proportion of patients achieving an improvement on VAS at Week 28 for patient's global disease activity.
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement of 10 mm for patient's global assessment of psoriasis and arthritis disease activity (VAS).	• Proportion of patients achieving an improvement on VAS at Week 28 for patient's global assessment of psoriasis and arthritis disease activity.
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving MDA.	• Proportion of patients achieving MDA at Week 28.

Objectives	Endpoints
• The mean change from Baseline on secukinumab 300 mg s.c. is higher compared to ustekinumab 45/90 mg s.c. at Week 28 for the LEI.	• Between-treatment difference in change from baseline to Week 28 for the LEI.
• The mean change from Baseline on secukinumab 300 mg s.c. is higher compared to ustekinumab 45/90 mg s.c. at Week 28 for the LDI.	• Between-treatment difference in change from baseline to Week 28 for the LDI.
• The mean change from Baseline on secukinumab 300 mg s.c. is higher compared to ustekinumab 45/90 mg s.c. at Week 28 for PsAQoL.	• Between-treatment difference in change from baseline to Week 28 in the PsAQoL.
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement of ≥ 4 points for FACIT-Fatigue©.	• Proportion of patients achieving a FACIT-Fatigue® response at Week 28.
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving a DLQI 0/1 response.	• Proportion of patients achieving a DLQI response of 0/1 at Week 28.
• To evaluate the safety and tolerability of secukinumab 300 mg s.c. compared to ustekinumab 45/90 mg s.c. as assessed by vital signs, clinical laboratory values, and AE monitoring.	• Number and proportion of patients with treatment-emergent AEs as well as descriptive description of vital signs and clinical laboratory values.

[redacted]

[redacted] E: adverse event, BSA: body surface area, [redacted] DLQI: Dermatology Life Quality Index, [redacted] EULAR: European League Against Rheumatism, FACIT-Fatigue©: Functional Assessment of Chronic Illness Therapy-fatigue, HAQ-DI©: Health Assessment Questionnaire-Disability Index, LDI: Leeds Dactylitis Index, LEI: Leeds Enthesitis Index, , MDA: Minimal Disease Activity, PASI: Psoriasis Area Severity Index, [redacted] PsAQoL: Psoriatic Arthritis Quality of Life, s.c.: subcutaneously, [redacted] SJC: Swollen Joint Count, [redacted] TJC: Tender Joint Count, VAS: Visual Analog Scale,

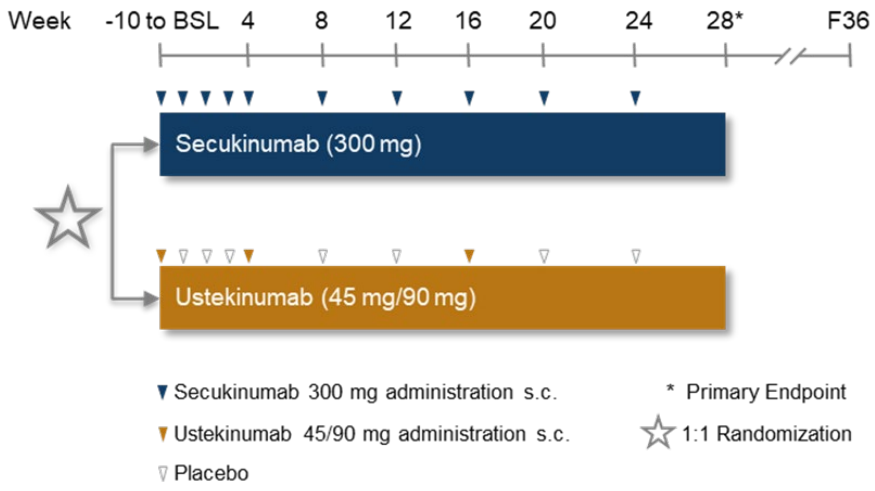
3 Study design

This is a randomized, double-blind, active-controlled, multicenter study involving 310 adult patients with PsA who failed TNFα inhibitor treatment. The aim of the study is to demonstrate that the efficacy of secukinumab is superior to ustekinumab in terms of achieving an improvement in health assessment questionnaire-disability index (HAQ-DI©) response ≥ 0.35 versus Baseline. Patients will be randomized equally to one of the following treatment groups (see Figure 3-1):

- Secukinumab 300 mg s.c. for administration at Week 0, 1, 2, 3, 4 followed by dosing every 4 weeks thereafter (i.e. at Week 8, 12, 16, 20 and 24).
- Ustekinumab 45 mg s.c. (or 90 mg s.c. if body weight > 100 kg) for administration at Week 0 and Week 4 followed by dosing 12 weeks later at Week 16. Placebo to secukinumab will be administered at the respective secukinumab dosing time points, i.e. at Week 1, 2, 3, 8, 12, 20 and 24.

The study will include a Screening period of up to 10 weeks, a treatment period of 28 weeks with the primary endpoint at Week 28, and a follow-up period of 8 weeks.

Figure 3-1 Study Design



BSL: Baseline, F: Follow-up

4 Rationale

4.1 Rationale for study design

The randomized, double-blind, active control, multicenter, parallel-group design used in this study is in alignment with clinical trials in the development program for secukinumab, as well as with other biologics in this disease area, and is also in compliance with the European Medicines Agency (EMA) guidelines on PsA trials (EMA 2005). As described in Section 1.1, this study aims to demonstrate the superiority of secukinumab to ustekinumab for treating patients with PsA who have failed at least one initial TNFα inhibitor treatment based on the proportion of patients achieving a HAQ-DI© response ≥ 0.35 versus Baseline. The trial will close the scientific gap regarding this population in a head-to-head setting and support treatment

decisions in light of recent German HTA process recommendations. Secukinumab has already been shown to be superior to ustekinumab in the treatment of moderate-to-severe psoriasis (Blauvelt et al 2017, Bagel et al 2018).

4.2 Rationale for dose/regimen and duration of treatment

The dose regimens selected for secukinumab and ustekinumab are as per the approved label for the respective drugs in various countries i.e. 300 mg for secukinumab (the recommended dose within approved product labelling in the anti-TNF-IR population), and dosing per weight group for ustekinumab.

Secukinumab will be administered at a dose of 300 mg administered subcutaneously with a weekly loading regimen (Baseline/randomization, Week 1, Week 2, and Week 3) followed by treatment every 4 weeks thereafter (starting at Week 4) per approved dose of secukinumab in PsA for anti-TNF-IR. The dosage of 300 mg has been reported to be effective and safe in all approved indications including PsA (McInnes et al 2017, Mease et al 2018).

Ustekinumab will be administered at Baseline, Week 4 and then every 12 weeks as per the approved dose regimen for treatment of patients with PsA: for patients weighing ≤ 100 kg, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks; for patients weighing >100 kg, alternatively a dose of 90 mg can be applied initially and 4 weeks later, followed by 90 mg every 12 weeks. Safety and efficacy have been positively proven in several trials including anti-TNF-IR patients (Ritchlin et al 2014).

In previous studies, 24 weeks served as duration for the primary endpoint at which significant results vs. placebo were shown in PsA secukinumab trials as well as in ustekinumab trials (McInnes et al 2017, Mease et al 2018, Ritchlin et al 2014). 28 weeks for the primary endpoint were chosen in this trial as this is the first time point beyond 24 weeks where secukinumab and ustekinumab treatment would be applied according to the approved application interval of secukinumab and ustekinumab (every 4 weeks for secukinumab and every 12 weeks for ustekinumab). With the primary endpoint at week 28, the injection interval is at the end for both drugs without having an advantage/a disadvantage for either of the drugs.

Formulation to be used

Secukinumab 300 mg (2 x 150 mg/1 mL), placebo liquid, and ustekinumab 45 mg/0.5 mL and 90 mg/1 mL (formulation approved for PsA) will be provided in single-use pre-filled syringes (PFS).

4.3 Rationale for choice of control drugs (comparator/placebo)

An active comparator group is necessary to evaluate whether secukinumab is superior to an approved therapy in PsA after anti-TNFα failure. The parallel-group controlled design is the most appropriate method to compare the two therapies and is consistent with the study of other biologics in the treatment of PsA.

Ustekinumab has been selected as the active comparator in this study. Ustekinumab is a fully human monoclonal anti-human IL-12/23 antibody of the IgG1/κ-class, which has been commercially available for a number of years and has proven to be a safe and efficacious

treatment for PsA in anti-TNFα naive and IR patients (PSUMMIT 1, PSUMMIT 2; Ritchlin et al 2014, McInnes et al 2019).

Superiority of secukinumab to ustekinumab has already been demonstrated in the treatment of moderate-to-severe psoriasis (Blauvelt et al 2017, Bagel et al 2018). Up to date, no data are available comparing secukinumab with ustekinumab in a head-to-head setting in PsA patients who failed prior anti-TNFα treatment. Additionally, ustekinumab is now listed as an appropriate comparator in the German HTA process for PsA anti-TNF-IR.

In order to maintain the study blind, patients assigned to ustekinumab will receive placebo secukinumab PFS injections at the corresponding secukinumab administration time points. An additional placebo injection will accompany the respective ustekinumab injection as ustekinumab is administered in one syringe compared to 300 mg secukinumab which is applied in two 150 mg syringes.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

Secukinumab demonstrated clinically meaningful sustained and statistically significant efficacy for the treatment of patients with active PsA through all components of joint and skin disease, physical function, health-related quality of life (HRQoL) and structural damage. Pre-specified endpoints adjusted for multiple testing demonstrated the superiority of secukinumab 150 mg and 300 mg regimens compared to placebo. The American College of Rheumatology (ACR)20 response achieved at 24 weeks with 150 mg s.c. regimen was comparable to the responses with 300 mg s.c. regimen in anti-TNFα naive patients (FUTURE 2, FUTURE 5; McInnes et al 2015, Mease et al 2018). As in the psoriasis program, secukinumab 150 mg s.c. and 300 mg s.c. provided greater improvements than placebo in PsA patients with concomitant psoriasis. Overall, secukinumab is efficacious and demonstrates a rapid onset of response in achieving clinically meaningful improvements in key clinical domains of PsA disease. These domains include signs and symptoms, skin disease, structural damage, physical function and QoL. The 150 mg s.c. regimen provides rapid, superior efficacy for most patients, and the 300 mg s.c. regimen offers increased benefit for anti-TNFα IR patients and in patients with moderate-to-severe psoriasis. Efficacy results were sustained over time in all studies.

The safety profile observed in the latest Developmental Safety Update Report (DSUR No. 9) period (covering 26-Jun-2018 to 25-Jun-2019) is in line with the current known safety profile of secukinumab in PsA, moderate-to-severe psoriasis, and axial spondyloarthritis.

For all 3 indications, secukinumab has shown an imbalance vs. placebo in total AEs, which was driven by infections, mainly non-serious upper respiratory tract infections during the placebo-controlled epoch of the trials (12 to 16 weeks depending on the protocol). This imbalance was not translated into infection serious AEs (SAEs) and there was also no difference between 300 mg and 150 mg secukinumab in the overall rate of infections or in upper respiratory tract infections. In all indications, Candida infections, mainly oral candidiasis, were more frequent with secukinumab when compared to placebo, but the cases were generally mild or moderate in severity, non-serious with no reports of chronic or systemic disease in any treatment group

and responsive to standard treatment. No serious opportunistic infections were reported. No tuberculosis (TB) reactivation or viral hepatitis reactivation were observed in clinical trials, regardless of indication (PsA, psoriasis or axial spondyloarthritis).

There is a small increase in neutropenia cases with secukinumab compared to placebo, but most cases were mild, transient and spontaneously reversible and without a temporal relationship to serious infections.

The incidence of hypersensitivity AEs was slightly higher with secukinumab compared with placebo, with the difference being mostly due to mild to moderate urticaria and eczema, which were not associated with systemic symptoms.

The incidence of selected rare events of interest (major adverse cardiovascular events (MACE) and malignancies) adjusted for exposure over 52 weeks was comparable to placebo in clinical trials across multiple indications.

There was no clear association between treatment with secukinumab and new onset of inflammatory bowel disease (IBD). A pooled secukinumab safety analysis of over 7300 patients across 21 clinical trials showed only uncommon cases of IBD (Schreiber et al 2019). But, due to the potential involvement of the IL-17 pathway in the pathogenesis of the disease, it is not possible to rule out a potential increased risk of exacerbation.

The immunogenicity potential, i.e. of eliciting anti-drug antibodies (ADA), is higher for ustekinumab (up to 12.4%) than for secukinumab (<1%) (Stelara® package insert; Cosentyx® package insert). However, the presence of ADAs does not appear to be associated with development of adverse reactions or lack of efficacy for both ustekinumab and secukinumab.

Secukinumab has an acceptable safety profile for the intended use in adult patients. Secukinumab 300 mg was comparable to 150 mg and both doses showed comparable safety to placebo and etanercept over 52 weeks of treatment for psoriasis indication (Langley et al 2014). No dedicated head-to-head study was conducted with etanercept for spondyloarthritis indications.

Infections, neutropenia and hypersensitivity are important identified risks, while malignancies, MACE, Crohn's disease, and hepatitis B reactivation are important potential risks. Interaction with live vaccines is an important potential interaction (and also included as an important potential risk).

No new safety signal was identified in the reporting period.

The benefit-risk relationship for secukinumab remains positive for the treatment of PsA, as well as other indications, and justifies unaltered continuation of the development program.

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. Refer to the Investigator's Brochure (IB) for further details.

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

Taking into account the individual risks as outlined above, the expected risk profile of secukinumab from its mechanism of action is anticipated to be similar or improved compared to the other approved inflammatory cytokine-targeting therapies. The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and extensive guidance to the investigators provided by Novartis and in the current version of the IB for secukinumab. Based on the overall favorable risk-benefit assessment, the current trial with secukinumab (and the comparator ustekinumab) is justified.

5 Population

The study population will consist of a representative group of 310 male or female patients at least 18 years of age, fulfilling the Classification criteria for Psoriatic Arthritis (CASPAR) (Appendix 1) and who have shown previous inadequate response or intolerance to TNFα inhibitors.

The study population will be comprised of the subjects who have passed screening assessments and who comply with eligibility criteria. Subjects can be re-screened, no study related re-screening procedures should be performed before re-consent by the subject. Mis-randomized subjects will not be re-screened.

5.1 Inclusion criteria

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

1. Informed consent must be obtained before any assessment is performed.
2. Male or non-pregnant, non-lactating female patients at least 18 years of age.
3. Diagnosis of PsA as classified by CASPAR criteria (see Appendix 1) for at least 6 months before randomization.
4. Active PsA at baseline defined as ≥ 3 tender joints out of 68 and ≥ 3 swollen joints out of 66 (dactylitis of a digit counts as one joint each).
5. Inadequate response or intolerance to previous or current treatment with at least one TNFα inhibitor administered at an approved dose for the given duration according to the respective Summary of Product Characteristics (SmPC).
6. Inadequate response or intolerance to conventional disease modifying anti-rheumatic drugs (cDMARDs) and to at least one TNFα inhibitor must have been documented in the patient's medical history or reported by the patient or determined by the investigator at Screening.
7. Diagnosis of active plaque psoriasis, with at least one psoriatic plaque of ≥ 2 cm diameter and/or nail changes consistent with psoriasis and/or documented history of plaque psoriasis.
8. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies negative at screening.
9. Patients taking methotrexate (MTX) ≤ 30 mg/week are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization and should remain on a stable dose up to Week 28.
10. Patients on MTX must be on folic acid supplementation at randomization.

11. Patients who are on a disease modifying anti-rheumatic drug (DMARD) other than MTX must discontinue the DMARD 4 weeks prior to the randomization visit except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine wash-out has been performed.
12. Patients who are regularly receiving non-steroidal anti-inflammatory drugs (NSAIDs) as part of their PsA therapy are required to be on a stable dose for at least 2 weeks before study randomization and should not increase the dose up to Week 28.
13. Patients receiving corticosteroids must be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 28.

5.2 Exclusion criteria

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

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
2. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and minimum 16 weeks or longer if local label requires it after the last dose (e.g. 20 weeks for secukinumab, 15 weeks for ustekinumab in the European Union (EU)).

   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 investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male sterilization (at least 6 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).
   - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking the investigational drug.

   In case local regulations deviate from the methods listed, local regulations apply and will be described in the informed consent form (ICF).

   Women are considered post-menopausal and not of child-bearing potential if they have had at least 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 child-bearing potential.

3. Previous exposure to secukinumab, ustekinumab or any other biologic drug directly targeting IL-17, IL-17 receptor, IL-12 or IL-23.
4. Patients for whom the use of secukinumab or ustekinumab is contraindicated.
5. Use of any other investigational drug within 4 weeks or within a period of 5 half-lives of the investigational treatment prior to the Baseline Visit, whichever is longer, until the expected pharmacodynamic effect has vanished. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g., alemtuzumab (Campath®), anti-CD4, anti-CD5, anti-CD3, and anti-CD19).
6. Chest X-ray or chest magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process obtained within 3 months prior to Screening and evaluated by a qualified physician.
7. Patients receiving high potency opioid analgesics including but not limited to methadone, hydromorphone, and morphine.
8. Ongoing use of prohibited psoriasis treatments/medications (e.g., topical corticosteroids or ultraviolet therapy at randomization). The following wash out periods need to be observed:
    a. Oral or topical retinoids: 4 weeks
    b. Photochemotherapy (e.g. PUVA): 4 weeks
    c. Phototherapy (UVA or UVB): 2 weeks
    d. Topical skin treatment (except in face, eyes, scalp and genital area during screening; only corticosteroids with mild to moderate potency): 2 weeks.
9. History of hypersensitivity to any of the study drugs or excipients or to drugs of similar chemical classes.
10. Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization.
11. Any therapy by intra-articular injections (e.g., corticosteroid) within 4 weeks before randomization.
12. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy.
13. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the subject and/or places the subject at unacceptable risk for participation in an immunomodulatory therapy.
14. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV) and uncontrolled diabetes.
15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFTs) such as aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), alkaline phosphatase or serum bilirubin. The investigator should be guided by the following criteria:

a. Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible and in all cases, at least prior to enrollment/randomization, to rule out any possible lab error.
b. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

16. History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a serum creatinine level exceeding 1.8 mg/dL (159.12 μmol/L).
17. Screening total white blood cell (WBC) count <3,000/μL, or platelets <100,000/μL or neutrophils <1,500/μL or hemoglobin <8.5 g/dL (85 g/L).
18. Active systemic infections during the last two weeks (exception: common cold) prior to randomization.
19. History of ongoing, chronic or recurrent infectious disease or evidence of TB infection as defined by a positive QuantiFERON TB-Plus test. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active TB. If presence of latent TB is established then treatment according to local country guidelines must have been initiated prior to enrollment.
20. Live vaccinations within 6 weeks prior to Baseline or planned vaccination during study participation until 12 weeks after last study treatment administration.
21. Proven infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization.
22. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed).
23. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the subject unsuitable for the trial.
24. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
25. 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.
26. Donation or loss of 400 mL or more of blood within 8 weeks before randomization.
27. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

The following study drugs will be used:

- Investigational treatment
  - Secukinumab 300 mg, 2 x 1 mL liquid formulation in a PFS
- Control treatment
  - Secukinumab placebo, 1 mL liquid formulation in a PFS
  - Ustekinumab 45 mg, 0.5 mL or 90 mg, 1 mL liquid formulation in a PFS

Investigational treatment:

Secukinumab for s.c. injection is provided in a PFS containing 150 mg secukinumab. Each 300 mg dose is given as 2 s.c. injections of 150 mg.

Control treatment:

- Secukinumab placebo: secukinumab placebo to 150 mg secukinumab for s.c. injection is provided in a matching PFS. Each PFS contains a mixture of inactive excipients, matching the composition of the secukinumab 150 mg dose.
- Ustekinumab is provided in a PFS containing 45 mg or 90 mg of ustekinumab for s.c. injection. Patients weighing ≤ 100 mg at Baseline will receive a dose of 45 mg, patients weighing > 100 kg at Baseline 90 mg according to the label.

Secukinumab 150 mg PFS and secukinumab placebo PFS will be supplied by Novartis.

Ustekinumab 45 mg and 90 mg PFS will be supplied by Novartis.

All study drugs will be labelled appropriately.

The removable cap of the secukinumab PFS contains a derivative of natural rubber latex. Although no natural rubber latex is detected in the cap, the safe use of the secukinumab 1 mL PFS in latex-sensitive individuals has not been studied.

6.1.2 Additional study treatments

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

6.1.3 Treatment arms

Patients will be randomized to one of the following 2 treatment arms in a ratio of 1:1. In order to achieve a balanced weight distribution in each treatment arm, randomization in these 2 arms will be stratified by body weight (≤ 100 kg and > 100 kg) at Baseline. The weight must be ascertained using a calibrated scale and the correct dosage determined by the PI.

- **Secukinumab arm**: will receive a dose of secukinumab 300 mg s.c. which consists of 2 injections of the 150 mg PFS at a frequency shown in Table 6-1.
- **Ustekinumab arm**:
  - Patients weighing ≤ 100 kg at Baseline will receive a dose of 45 mg ustekinumab s.c., which consists of one injection of the 45 mg PFS + one placebo s.c. injection at a frequency shown in Table 6-1.
  - Patients weighing >100 kg at Baseline will receive a dose of 90 mg ustekinumab s.c., which consists of one injection of the 90 mg PFS + one placebo s.c. injection at a frequency shown in Table 6-1.

In order to maintain the blind, placebo injections matching the secukinumab 150 mg PFS will be given to patients in the ustekinumab arm at various time points, as it can be seen in Table 6-1 so that all patients will receive 2 s.c. injections at each dosing time point.

Furthermore, the PFS for secukinumab and ustekinumab have a different outward appearance. Therefore, as this is a double-blind study, the dispensing and administration of the study treatments will be performed at the study site by suitably qualified unblinded personnel who are not otherwise involved in the study conduct while patients and all other study site personnel will be blinded.

Table 6-1 Overview of treatment during the study – type and number of injections

	Screening	Treatment Period										EOS	FUP
Week (relative to randomization)	**-10 to BSL**	**R**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**36**
Visit number	**SV**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Secukinumab 300 mg													
Active injection[1]	-	2	2	2	2	2	2	2	2	2	2	-	-
Ustekinumab[2]													
Patient ≤ 100 kg													
Active injection[2]	-	1	-	-	-	1	-	-	1	-	-	-	-
Placebo injection[3]	-	1	2	2	2	1	2	2	1	2	2	-	-
Patient > 100 kg													
Active injection[2]	-	1	-	-	-	1		-	1	-	-	-	-
Placebo injection[3]	-	1	2	2	2	1	2	2	1	2	2	-	-

BSL = Baseline, EOS = end of study, FUP = follow-up, R = Randomization, SV = Screening Visit, V = Visit

[1] Secukinumab 150 mg PFS: patients randomized to secukinumab will receive 2 active injections;

[2] Ustekinumab dose based on body weight at Baseline: 45 mg for patient ≤ 100 kg (1 active injection); 90 mg for patient > 100 kg (1 active injection)

[3] Secukinumab placebo PFS

6.1.4 Treatment duration

Study treatment (secukinumab or ustekinumab/placebo) will be administered from randomization until Week 24 (last dose at Week 24, EOS at Week 28).

6.2 Other treatment

6.2.1 Concomitant therapy

The investigator should instruct the patient to notify the study site about any new medications, over-the-counter drugs, supplements, and vitamins administered after the patient is enrolled into the study. All medications (other than study treatment), procedures and significant non-drug therapies (including physical therapy and blood transfusions) must be recorded on the Prior and Concomitant medications or Procedures and Significant Non Drug Therapy electronic case

report form (eCRF). The reason, name of the drug, procedure or non-drug therapy should be listed.

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, Novartis should be contacted to determine if the patient should continue participation in the study. Guidelines for the use of specific medications are provided below.

The patient is not allowed to participate in other clinical trials during the duration of the actual study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Methotrexate

Patients taking MTX (up to 30 mg/week) are allowed to continue their medication. They must be on a stable dose for at least 4 weeks before randomization and should remain on this dose until Week 28.

Systemic corticosteroids

Treatment with systemic corticosteroids is permitted up to a maximum daily dosage of 10 mg prednisone equivalent and if the dose was stable within the 2 weeks preceding randomization. The patient should remain on a stable dose until Week 28. Higher-dose, time-limited corticosteroid courses (bursts) may be permitted for exacerbations of medical conditions unrelated to PsA (e.g., asthma, chronic obstructive pulmonary disease, contact dermatitis) after randomization.

Corticosteroid dose reductions below 10 mg prednisone equivalent are permitted during the study.

However, any change in the dose of oral corticosteroids during the trial should be recorded on the corresponding eCRF.

Intra-articular corticosteroids are not permitted within 4 weeks prior to Baseline and up to Week 28. The joints injected with intra-articular corticosteroids will be assessed as both swollen and tender in the SJC and TJC, from injection time onwards.

Non-steroidal anti-inflammatory drugs (including selective COX-2 inhibitors), low strength opioids and acetaminophen/paracetamol

Patients on regular use of NSAIDs or paracetamol/acetaminophen should be on stable dose for at least 2 weeks before randomization to allow inclusion.

Patients taking NSAIDs, low strength opioids, or paracetamol/acetaminophen *pro re nata*/as required (PRN) within the 2 weeks before randomization can continue to do so after randomization, however, they have to refrain from any intake during at least 24 hours before a visit with disease activity assessment.

When indicated, a reduction of NSAIDs is permitted during the study.

After Week 28, a change in the NSAIDs, low strength opioids or paracetamol/acetaminophen treatment regimen is permitted. Any change of the NSAIDs, low strength opioids or paracetamol/acetaminophen treatment during the trial should be recorded on the corresponding eCRF.

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-2 is NOT allowed after the start of the washout period unless specified otherwise below or in Section 9.1.1.

Live vaccines should not be given until 12 weeks after last study treatment administration.

Table 6-2 Prohibited medication

Medication	Action (after randomization)	Washout period (before randomization)
Any biologic drugs, including but not limited to biologic drugs targeting IL-17, IL-17 receptor, IL-12 or IL-23 (except study medication)	Discontinue investigational treatment	Biologics for PsA and psoriasis: never Biologics for other indications: 16 weeks
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents [e.g., alemtuzumab (Campath), anti-CD4, anti-CD5, anti-CD3, and anti-CD19]	Discontinue investigational treatment	Never
cDMARDs other than MTX (≤ 30 mg/week) including apremilast and tsDMARDs (JAK inhibitors)	Discontinue investigational treatment	4 weeks
Leflunomide	Discontinue investigational treatment	8 weeks
Leflunomide with cholestyramine washout	Discontinue investigational treatment	4 weeks
Any investigational treatment or participation in any interventional trial	Discontinue investigational treatment	4 weeks or 5 half-lives (whichever is longer)
Increasing dose of NSAIDs (selective COX-2 inhibitors)	Discontinuation of investigational treatment may be required on a case by case basis. (Dose increase allowed after Week 28)	2 weeks
Analgesics other than NSAIDs, paracetamol/acetaminophen, and low strength opioids PRN	Discontinue investigational treatment	2 weeks

Medication	Action (after randomization)	Washout period (before randomization)
Systemic corticosteroids > 10 mg prednisone equivalent (until Week 28)*	If administered due to a medical urgency unrelated to the patient's arthritis, study treatment should be interrupted until the steroid is discontinued. If administered not for a medical urgency or related to the patient's arthritis, then discontinuation of investigational treatment may be required on a case by case basis	2 weeks
Increasing dose of systemic corticosteroids ≤ 10 mg prednisone equivalent (until Week 28)*	Discontinuation of investigational treatment may be required on a case by case basis. (Dose adjustments allowed after Week 28)	2 weeks
Intra-articular corticosteroids injections, (until Week 28)*	Discontinue investigational treatment, (see Section 9.1.1)	4 weeks
Intramuscular or intravenous corticosteroid treatment	Discontinuation of investigational treatment may be required on a case by case basis	4 weeks
Live vaccinations	If administered due to a medical urgency, study treatment should be interrupted for 4 months. If administered not for a medical urgency then discontinue investigational treatment	6 weeks
Oral or topical retinoids	Discontinue investigational treatment	4 weeks
Photochemotherapy (e.g. PUVA)	Discontinue investigational treatment	4 weeks
Phototherapy (UVA or UVB)	Discontinue investigational treatment	2 weeks
Topical skin treatments (except in face, eyes, scalp, genital area; only cortico-steroids with mild to moderate potency)	Discontinue investigational treatment	2 weeks
Medical cannabis	Discontinue investigational treatment	2 weeks

CD: Cluster of Differentiation, COX: cyclooxygenase, cDMARDs: conventional synthetic Disease Modifying Anti-Rheumatic Drugs, IL: Interleukin, JAK: Janus Kinase, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, PRN: *pro re nata* (as required), PsA: psoriatic arthritis, PUVA: psoralen ultraviolet light A, TNFα: tumor necrosis factor alpha, tsDMARDs: targeted synthetic Disease Modifying Anti-Rheumatic Drugs, UVA: ultraviolet A, UVB: ultraviolet B

* see details about corticosteroid management in Section 6.2.1

6.2.2.1 Leflunomide wash-out with cholestyramine

In case of leflunomide treatment before study randomization, a drug wash-out of 8 weeks must be performed. However, another wash-out procedure can be considered. Cholestyramine may be given orally at a dose of 8 g three times daily (t.i.d) to wash out leflunomide. Cholestyramine has been shown to reduce plasma levels of the active leflunomide metabolite by approximately 40% in 24 hours and by 49% to 65% in 48 hours, in 3 healthy volunteers. The administration of cholestyramine is recommended in patients who require a drug elimination procedure. If a patient receives 8 g t.i.d. for 11 days, the patient can be safely randomized 4 weeks after the beginning of the 11-day treatment period.

6.2.3 Rescue medication

Rescue medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a patient is experiencing either no benefit from participation in the trial or worsening/exacerbation of their disease.

Rescue medication must not be used before completion of Week 28 assessments (see Section 3). Please see Section 6.2.1 and Section 6.2.2 for details. No patient will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease and may continue investigational treatment if treated with prohibited medications (please see Section 6.2.2). Patients who discontinue investigational treatment should continue to attend all subsequent scheduled visit assessments unless informed consent is withdrawn. If study investigational treatment is discontinued, patients may take study prohibited medication under the investigator's guidance and per locally approved prescribing information.

Efficacy and safety will be assessed in detail at every study visit and patients who are deemed by the investigator not to be benefiting from study treatment, or for any reason on the patient's own accord, will be free to discontinue study participation at any time.

Use of rescue medication must be recorded on the corresponding eCRF.

6.3 Patient numbering, treatment assignment, randomization

6.3.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number (Patient ID). The center number is assigned by Novartis to the investigative site. When the patient has signed the informed consent form, the investigator or his/her staff will create a new patient record in the eCRF and provide the identifying information for the patient. The eCRF will then assign the patient number. Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized, the reason must be documented in the eCRF immediately. In addition, the Screening Log should be completed for these patients.

6.3.2 Treatment assignment, randomization

At the randomization visit (Baseline) all eligible patients will be given an available randomization number that assigns them to one of the two treatment arms. It is ensured that treatment assignment is unbiased and concealed from patients and investigator staff. Subsequently, the investigator will enter the randomization number in the eCRF.

A patient randomization list will be produced by or under the responsibility of Novartis Biometrics Department using a validated system ensuring random assignment of treatment groups to randomization numbers in the specified 1:1 ratio (secukinumab group, ustekinumab group). The randomization scheme will be reviewed and locked after approval. According to the recommendations given in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 Guideline "Statistical Principles for Clinical Trials", the used block length is specified in a separate document which will be with-held from the study centers. The randomization list will be kept sealed in a secure location.

All study sites will be provided with a given set of sealed allocation cards.

At the Randomization Visit, the investigator will assign each patient who meets all the inclusion criteria and does not fulfill any of the exclusion criteria to the lowest available randomization number, open the corresponding treatment allocation card and treat the patient with the treatment noted on this card (i.e. secukinumab treatment or ustekinumab treatment).

In order to achieve a balanced weight distribution in each treatment arm, randomization in these 2 arms will be stratified by body weight assessed at Day 1 (Baseline visit). The weight will not be further controlled in following visits. Stratification ensures a balanced allocation of patients to treatment groups within the 2 weight strata: "body weight ≤ 100 kg" or "body weight > 100 kg". It is expected that approximately 40% of the patients will be in the upper weight stratum.

6.4 Treatment blinding

All data up to Week 36 (Final Visit) will be collected with the Novartis clinical trial team (or delegates), investigators/site personnel evaluating patients and patients blinded to treatment allocation. All blinded site personnel, including the assessor performing the study assessments will remain blinded to individual treatment allocation until after final database lock using the following methods:

- Randomization data will be kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:
  - DSM (Drug Supply Management)
- Study medication will be dispensed by an unblinded qualified site personnel who is independent of those involved in the assessment of study patients. In addition, the unblinded qualified site personnel will store study medication and keep medication records containing unblinded information in a separate area to which blinded staff would not have access.
  - Study treatments will be administered by an "independent study drug administrator": an unblinded suitably qualified individual (nurse, physician, or other unblinded qualified site personnel) who is not responsible for any aspect of patient assessment or follow-up. The "Independent study drug administrator" could be the same person dispensing the drug if suitably qualified to perform both activities.
  - Prior to the administration, the unblinded site personnel will put in place all methods e.g. physical barriers as agreed with the patient and being available at the site to prevent patient seeing the appearance of their study treatment.

- The individual administering study treatment will be advised to refrain from making any comments to study staff or to other patients regarding the appearance of study treatments.
- The procedural details relating to treatment blinding and blinded drug administration will be described in a manual which will be provided separately.

In the event that the packaging of a study treatment has a broken seal, this information will be documented, along with a reason (if applicable) and the medication number so that the syringe will not be available to dispense to another patient.

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

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

6.5 Dose escalation and dose modification

Investigational treatment dose adjustments are not permitted. For patients who are unable to tolerate the protocol-specified dosing scheme (including patients who in the opinion of the investigator are at significant safety risk unless dosing is temporarily interrupted), investigational treatment interruption is permitted in order to keep the patient on study drug. In such cases, investigational treatment should be interrupted only during the time that a risk is present and ongoing. Investigational treatment can be restarted at the next scheduled visit after resolution of the safety risk.

The effect of secukinumab or ustekinumab on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. The elimination of ustekinumab may take up to 15 weeks (STELARA SmPC); in case a live vaccine has been administered due to a medical urgency, study treatment should be interrupted for 15 weeks.

Any investigational treatment interruption must be recorded on the corresponding eCRF.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

All dates and times of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF. Up to the final database lock, compliance will be assessed by unblinded field monitor at each visit using PFS (secukinumab, ustekinumab and placebo) counts and empty medication boxes/outer packaging and information provided by the unblinded qualified site personnel responsible for treatment dispensation and preparation of the study treatment.

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment 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

is to be retained by Novartis and one set 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 dependable procedure in place to allow access to the emergency code break cards at any time in case of emergency.

Furthermore he/she needs to provide a telephone number (e.g. a mobile number) by which he/she can be reached throughout the trial in case of an emergency unblinding request for one of his/her patients 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 Novartis (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. As per Novartis standard operating procedures (SOPs) it is one of the primary responsibilities of each investigator to be available in case of an urgent emergency unblinding for one of his/her patients.

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

Study drug must be discontinued after emergency unblinding.

6.7 Preparation and dispensation

Each study site will be supplied by Novartis with secukinumab and placebo treatment in packaging of identical appearance.

Ustekinumab 45 mg and 90 mg PFS will be supplied by the Novartis DSM team.

The secukinumab and ustekinumab and placebo treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 2 treatment arms. The unblinded qualified site personnel will identify the study drug package(s) to dispense to the patient using the medication number on the label. Immediately before dispensing the study drug to the patient, the unblinded qualified site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) containing the patient's unique Patient ID. Immediately after dispensing the study drug to the patient, investigator staff will access the eCRF to confirm administration of the assigned medication pack.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

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

The study treatments, i.e. secukinumab PFS 150 mg, ustekinumab 45 mg / 90 mg PFS (uninterrupted cold chain) and placebo must be stored in a locked refrigerator at 2-8°C, and protected from light and must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations. Study treatments should not be frozen.

The unblinded qualified site personnel 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 unblinded monitors during site visits or remotely and at the completion of the trial.

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

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the eCRF.

Secukinumab solution, placebo solution and ustekinumab solution will be provided in PFSs for s. c. injection.

All doses of study treatment are to be administered by an unblinded qualified person at the study site and should be performed after the study assessments for the visit have been completed. The first study treatment administration will occur at the randomization visit after inclusion/exclusion criteria have been confirmed, all study scheduled assessments have been performed and the scheduled blood samples have been drawn.

At all study site visits when pre-dose blood samples have to be drawn (Table 8-1), the study treatment will be injected only after the blood samples have been taken. At all site visits when study assessments need to be done, all study assessments, should be completed prior to the injection of study treatment.

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 the regulatory needs of the respective countries.

The investigator must promote compliance by instructing the patient to attend the study visits as scheduled and by stating that compliance is necessary for the patient's safety and the validity of the study.

Study treatment administration

All study treatment must be administered at the site and will be administered by unblinded site personnel not responsible for any aspect of patient assessment or follow-up (Section 6.4). The study treatment solution must be injected in non-affected areas of the skin into the appropriate body site (thigh, abdomen, upper outer arm). If possible, throughout the trial administer the study treatment rotating the injection site from visit to visit and also for each injection at a given visit.

Instructions mentioned in Section 6.4 must be followed to avoid unblinding. The type and number of injections to be administered are detailed in Table 8-1.

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 a proposed ICF that complies with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB and/or Core Data Sheet. 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 child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the study assessments and 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. Every effort should be made to respect the time frame for the Week 28 visit. If for any reason the subject is a screen failure, the subject may be rescreened. There is no restriction on the number of times a potential subject may be re-screened or on how much time must pass from the date of screen failure and the date of re-screening. If a subject re-screens for the study, a new ICF has to be signed. The initial subject number allocated to the patient when signing the ICF is reused throughout the study excluding further re-screenings. For all subjects, the investigator/qualified site staff will record if the subject was re-screened and the reason for previous screen failure on the re-screening CRF. No screening failure log will be filled out for patients that finally were enrolled into study.
Patients who prematurely discontinue the study treatment (s.c. secukinumab or ustekinumab) 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 other than withdrawal of informed consent should be scheduled for the final visit to conduct the Week 28 assessments (4 weeks after the last study treatment administration of secukinumab, 12 weeks after the last administration of ustekinumab), then also return after additional 8 weeks for a final follow-up visit, corresponding to week 36 assessments.

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

Table 8-1 Assessment Schedule

Visit Name	**Screening**	**Baseline**	**Treatment Period**									**EOS**	**FUP**
Visit Number	**SV**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Week	**-10 to Baseline**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**36**
Inclusion/exclusion criteria	X	X											
Information and informed consent	X												
Relevant medical history/current medical condition	X												
Drug washout evaluation/instruction	X												
Demography	X												
Smoking history	X												
Cardiovascular medical history	X												
Psoriatic arthritis/psoriasis medical history and previous therapies	X												
Physical examination	S	S				S	S	S	S	S	S	S	
Vital signs	X	X				X	X	X	X	X	X	X	
Randomization		X											
Weight	X	X[1]											
Height	X												
QuantiFERON TB-Plus test	X												
Chest X-ray/MRI‡	X												
Serum pregnancy test	X												
Urine pregnancy test[2]		X					X		X		X		X
Prior/concomitant medication/non-drug therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events/serious adverse events (including injection site reactions)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X

Clinical laboratory variables (hematology, blood chemistry, urinalysis)[4, 5]	X	X				X	X		X		X	X	X
Lipids[5]		X					X		X		X	X	
ANA		X										X	
Anti-dsDNA		X										X	
Anti-CCP	X												
Rheumatoid factor	X												
Administration of s.c. study treatment at study site[6, 7, 8]		X	X	X	X	X	X	X	X	X	X		
Psoriatic arthritis assessment	X												
CASPAR criteria	X												
68 TJC/66 SJC	X	X				X	X	X	X	X	X	X	
Psoriasis assessment	X												
PASI		X	X	X	X	X	X	X	X	X	X	X	
BSA		X	X	X	X	X	X	X	X	X	X	X	
[redacted]													
HAQ-DI©		X		X		X	X	X	X	X	X	X	
Patient's global assessment of disease activity (VAS)		X				X	X	X	X	X	X	X	
Patient's assessment of PsA pain (VAS)		X	X	X	X	X	X	X	X	X	X	X	
Patient's global assessment of psoriasis and arthritis disease activity (VAS)		X				X	X	X	X	X	X	X	
[redacted]													
LEI		X				X	X	X	X	X	X	X	
LDI		X				X	X	X	X	X	X	X	
MDA		X				X	X	X	X	X	X	X	
[redacted]													

[redacted]													
FACIT-Fatigue© v4		X				X	X	X	X	X	X	X	
[redacted]													
DLQI		X				X	X	X	X	X	X	X	
PsAQoL		X				X	X	X	X	X	X	X	
[redacted]													
ESR[2]		X		X		X	X	X	X	X	X	X	
[redacted]													

‡ Chest X-ray/MRI: If subjects do not have a chest X-ray available within 3 months of screening, an X-ray should be performed after it is certain the subject meets inclusion/exclusion criteria in order to minimize unnecessary exposure to X-ray radiation. At some sites selected by Novartis, the X-ray assessment may be replaced by chest MRI assessment.

[1] The correct dosage for ustekinumab will be determined by the PI regardless of knowing whether the patient will be randomized into the ustekinumab or the secukinumab arm

[2] Kits will be provided by central lab and test is to be performed locally

[3] AEs /SAEs occurring after the subject has provided informed consent must be reported

[4] Hepatitis B, hepatitis C and HIV serology testing, performed at local site during screening period prior to initiation of therapy. These assessments will be documented in source records only and will not be entered into the eCRF

[5] Sample must be obtained fasting

[6] The individual administering the investigational treatment must not be the investigator or study staff involved in safety and efficacy assessments

[7] For visits scheduled through Week 4, the study treatment should not be administered less than 7 days from the previous administration

[8] For visits scheduled after Week 4, the study treatment should not be administered less than 14 days from the previous administration

X = assessment to be recorded in the clinical database or received electronically from a vendor.
S = assessment to be recorded in the source documentation only.

[redacted]

[redacted] AE: adverse event, ANA: antinuclear antibody, Anti-dsDNA: anti-double stranded deoxyribonucleic acid, Anti-CCP: anti-cyclic citrullinated peptide, BSA: body surface area, CASPAR: Classification Criteria for Psoriatic Arthritis, [redacted], [redacted], [redacted] DLQI: Dermatology Life Quality Index, [redacted], ESR: erythrocyte sedimentation rate, EULAR: European League Against Rheumatism, FACIT-Fatigue©: Functional Assessment of Chronic Illness Therapy-fatigue, HAQ-DI©: Health Assessment Questionnaire-Disability Index, [redacted] DI: Leeds Dactylitis Index, LEI: Leeds Enthesitis Index, [redacted] MDA: Minimal Disease Activity, MRI: magnetic resonance imaging, [redacted] PASI: Psoriasis Area and Severity Index [redacted] PsAQoL: Psoriatic Arthritis Quality of Life, [redacted] SJC: swollen joint count, TB: tuberculosis, TJC: tender joint count, VAS: visual analog scale [redacted]

8.1 Screening

8.1.1 Information to be collected on screening failures

Patients who sign an ICF may discontinue from the study prior to randomization. These patients are considered Screening failures. The reason for Screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen failure patients. No other data will be entered into the clinical database for patients who are Screen failures, unless the patient experienced a SAE during the Screening phase.

Patients who are randomized and fail to start treatment, e.g. patients randomized in error, will be considered early terminators. The reason for early termination should be recorded on the appropriate CRF.

All patients who have signed informed consent and are randomized into the Treatment Period of the study will have all AEs occurring after informed consent is signed recorded on the Adverse Event eCRF.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.2 Patient demographics/other Baseline characteristics

All Baseline assessments should be performed prior to first study drug administration. These may occur during the Screening period or at the Baseline Visit depending on the assessment.

Patient demographic and Baseline characteristic data to be collected on all patients and recorded in the eCRF include:

- Date of birth, age, sex, race and source of patient referral.
- All relevant PsA/psoriasis and general medical history/current medical condition data until the start of investigational treatment, such as date of diagnosis of PsA/psoriasis, previous PsA/psoriasis therapies including treatment duration, cardiovascular medical history, smoking history and surgical sterilization for females if applicable.
- Documentation of inadequate response or intolerance to anti-TNFα treatment, type of used anti-TNFα, treatment duration and reason for discontinuation of the treatment

Whenever possible, diagnoses and not symptoms will be recorded.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

The efficacy outcome measures used in this study are standard measures used across all PsA trials.

- Health Assessment Questionnaire - Disability Index (HAQ-DI©)

- Psoriasis area and severity index (PASI)
- Patient's assessment of PsA pain intensity (VAS)
- Tender joint count (TJC)/swollen joint count (SJC)
- Patient's global assessment of disease activity (VAS)
- Patient's global assessment of psoriasis and arthritis disease activity (VAS)
- Minimal disease activity (MDA)
- Leeds enthesitis index (LEI)
- Leeds dactylitis index (LDI)
- [redacted]
- Body Surface Area (BSA)
- [redacted]

All efficacy assessments should be performed prior to administration of study treatment. Details relating to the administration of all patient reported outcomes (PROs) are provided in Appendix 2.

8.3.1 Health assessment questionnaire – disability index

The HAQ-DI© was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a patient's level of functional ability and activity restriction. The disability assessment component of the HAQ, the HAQ-DI©, assesses a patient's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to …" perform a particular task. Each item is scored on a 4-point scale from 0 to 3, representing normal, no difficulty (0), some difficulty (1), much difficulty (2), and unable to do (3).

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

8.3.2 Psoriasis area and severity index

The PASI (Fredriksson and Pettersson 1978; Weisman et al 2003; Gottlieb et al 2005) assesses the extent of psoriasis on 4 body surface areas (BSAs), i.e. head, trunk and upper and lower limbs, and the degree of plaque erythema, scaling and thickness. A PASI score 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 4 body regions is assigned a score of 0-4. The area covered by lesions

on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

- The neck is assessed as part of the head.
- The axillae and groin are assessed as part of the trunk.
- The buttocks are assessed as part of the lower limbs.

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

Table 8-2 The PASI scoring system

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

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

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

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

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

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 following formula:

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

where E = erythema; I = induration; D = desquamation; A = area; H = Head; U = Upper limbs; T = Trunk; and L = Lower limbs

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 investigator is responsible for collecting the components or scoring signs and total regional area. More information is provided in Appendix 5.

8.3.3 Patient's assessment of psoriatic arthritis pain

The patient's assessment of pain will be performed using a 100 mm VAS ranging from 'no pain' to 'unbearable pain' after the question '*Please indicate with a vertical mark (|) through the horizontal line the most pain you had from your psoriatic arthritis today'*.

8.3.4 Tender 68 joint count and swollen 66 joint count

Joint counts will be performed by an assessor(s) who must be well trained and part of the site personnel. Whenever possible, the same evaluator should perform these assessments at all visits.

The 68 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 10 metacarpophalangeal, 10 proximal interphalangeal, 8 distal interphalangeal joints of the hands, 2 hips, 2 knees, 2 talo-tibial, 2 mid-tarsal, 10 metatarsophalangeal, and 10 proximal interphalangeal joints of the feet. All of these except for the hips are assessed for swelling (Duarte-Garcia et al 2019). Joint tenderness and swelling are to be graded present (1) or absent (0). Synovial fluid and/or soft tissue swelling but not bony overgrowth represents a positive result for swollen joint count. Dactylitis of a digit in the foot or hand counts as one tender and swollen joint.

Data is recorded for tender and swollen joints (right or left side), i.e. a box (yes, no or not applicable), needs to be ticked for all joints.

In case a joint is injected with corticosteroids (see restrictions in Section 6.2.1) this joint will be assessed as both swollen and tender in the SJC and TJC, from injection time onwards.

[redacted]

8.3.6 Patient's global assessment of disease activity

The patient's global assessment of disease activity will be performed using a 100 mm (VAS) ranging from 'very good' to 'very poor' after the question '*Considering all the ways Psoriatic Arthritis affects you, please indicate with a vertical mark (|) through the horizontal line how well you are today'*.

8.3.7 Patient's global assessment of psoriasis and arthritis disease activity

Global disease activity: The patient's assessment of psoriasis and arthritis will be performed using a 100 mm VAS ranging from 'Excellent' to 'Poor' after the question *'Considering all the ways PSORIASIS and ARTHRITIS affects you, please indicate with a vertical mark (|) through the horizontal line how well you are doing over the past week'.*

8.3.8 Minimal disease activity

Proportion of patients achieving MDA (Coates et al 2010), defined as 5 **and** 7 (very low disease activity) of the following 7 criteria:

- ≤ 1 tender joint
- ≤ 1 swollen joint
- PASI ≤ 1 or BSA < 3%
- Patient's assessment of pain on VAS ≤ 15
- Patient's global assessment of disease (VAS) ≤ 20
- HAQ-DI© ≤ 0.5
- Tender entheseal points ≤ 1

8.3.9 Leeds enthesitis index

The LEI assessment will be performed by the independent assessor(s) who must be well trained and part of the site personnel. Whenever possible, the same evaluator should perform these assessments at all visits.

The LEI is a validated enthesitis index that uses 6 sites for evaluation of enthesitis: lateral epicondyle humerus left (L) + right (R), proximal achilles L + R and medial condyle femur L+R. The LEI demonstrated substantial to excellent agreement with other scores in the indication of PsA (Healy and Helliwell 2008).

Presence of enthesitis

If enthesitis is present with any of the 6 sites, the patient is counted as a patient with enthesitis.

8.3.10 Leeds dactylitis index

The LDI assessments will be performed by the independent assessor(s) who must be well trained and part of the site personnel. Whenever possible, the same evaluator should perform these assessments at all visits.

The LDI basic measures the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot, using a minimum difference of 10% to define a dactylitic digit (Helliwell et al 2005). The ratio of circumference is multiplied by a tenderness

score, using a modification of LDI, which is a binary score (1 for tender, 0 for non-tender). If both sides are considered involved, or the circumference of the contralateral digit cannot be obtained, the number will be compared to data provided in the standard reference tables (see Appendix 4). This modification is referred to as LDI basic and will be applied in this study. The LDI requires a finger circumference gauge or a dactylometer to measure digital circumference.

Dactylitis count

The dactylitis count is the number of fingers and toes with dactylitis, with a range of 0-20.

Presence of dactylitis

If dactylitis is present in any finger or toe, the patient will be counted as having dactylitis.

[redacted]

8.3.12 American College of Rheumatology response

The ACR response (Appendix 3) will be used to determine efficacy (Felson et al 1995). [redacted]

- [redacted]
- [redacted]
- [redacted]
  - Patient's global assessment of disease activity (measured on a VAS scale, 0-100)
  - [redacted]
  - Patient's assessment of PsA pain (measured on a VAS scale, 0-100)
  - HAQ-DI© score
  - Acute phase reactant ([redacted] ESR)

[redacted]

The ACR response is to be assessed at the visits/time points shown in Table 8-1.

[redacted]

[redacted]

[redacted]

8.3.15 Erythrocyte sedimentation rate

Blood for ESR, which is helpful in diagnosing inflammatory diseases and is used to monitor disease activity and response to therapy, will be obtained at scheduled visits as indicated in Table 8-1.

8.3.16 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are the standard measures used across many PsA trials.

8.4 Safety

Evaluation of all AEs and SAEs including injection site reactions, physical examination, vital signs and laboratory assessments will occur.

All blood draws and safety assessments should be done prior to study treatment administration. Appropriate safety assessments (e.g. evaluation of AEs and SAEs including injection site reactions) should be repeated after the dose is administered.

- Evaluation of AE/SAEs
- Physical examination
- Vital signs
- Height and weight
- QuantiFERON TB-Plus test
- Local tolerability (injection site reactions)
- Laboratory evaluations (hematology, clinical chemistry, lipid panel, urinalysis)

- Pregnancy and assessment of fertility

8.4.1 Physical examination

The physical examination will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological system.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present before signing the ICF must be included in the relevant medical history eCRF. Significant findings made after signing the ICF which meet the definition of an AE must be recorded in the Adverse Event eCRF.

8.4.2 Vital signs

Vital signs will include blood pressure and pulse rate measurements after 5 minutes rest in sitting position. If possible, vital signs assessments should be performed by the same study site staff member using the same validated device throughout the study.

8.4.3 Height and weight

Height in centimeters (cm) and body weight, to the nearest 0.1 kilogram (kg), in indoor clothing but without shoes, will be measured.

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

8.4.4 Tuberculosis screening

A QuantiFERON TB-Plus test is to be performed at Screening and the results should be known prior to randomization to determine the patient's eligibility for the trial. The test will be used to screen the patient population for latent tuberculosis infection.

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 TB
- If presence of latent TB is established then treatment according to local country guidelines must have been initiated.

The QuantiFERON TB-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.

X-ray or MRI of the chest

A chest X-ray (posteroanterior view) or MRI at Screening (or within 3 months prior to Screening) will be performed to rule out the presence of a pulmonary malignancy or infectious process, in particular, TB. The results must be known prior to randomization to determine the patient's eligibility for the study. These assessments will be documented in source records only and will not be entered into the CRF.

8.4.5 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed below (except urinalysis). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. For the identification of clinically notable values, see Appendix 6 and Appendix 7. All patients with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

8.4.5.1 Hematology

Hemoglobin, platelets, red blood cell (RBC), white blood cell (WBC) and differential white blood cell counts will be measured at scheduled visits.

8.4.5.2 Clinical chemistry

Serum chemistries will include glucose, urea, creatinine, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorus, total protein, albumin, and uric acid.

8.4.5.3 Urinalysis

Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments. The urinalysis results for standard parameters such as protein, glucose, blood, and WBCs will be recorded in the appropriate eCRF.

8.4.5.4 Lipid panel

A lipid profile including high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol, and triglycerides will be measured from a fasting blood sample.

8.4.6 Pregnancy and assessments of fertility

The study treatment 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 at Screening. All women who are not surgically sterile or post-menopausal (as defined in Section 5.2) 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 discontinue study treatment.

Assessments of fertility

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 child-bearing 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, FSH testing is required of any female patient regardless of reported reproductive/menopausal status at Screening/Baseline.

8.4.7 Tolerability of investigational treatments

Tolerability will be assessed by AEs, laboratory values, injection site reaction, and immunogenicity.

8.4.8 Additional parameters

Blood will be obtained at the first Screening Visit (Visit 1) for anti-cyclic citrullinated peptide (anti-CCP) antibodies and the rheumatoid factor (RF) assessment. Antinuclear antibody (ANA) and anti-double stranded deoxyribonucleic acid antibody (anti-dsDNA) antibodies will also be assessed at visits/time points indicated in Table 8-1.

8.4.9 Appropriateness of safety measurements

The safety measures used in this study are standard measures for assessing the safety of a biological drug in patients with PsA. A chest X-ray or MRI at Screening (or within 3 months prior to Screening) is performed to rule out the presence of a pulmonary malignancy of infectious process (in particular TB).

The total amount of radiation exposure that results from the Screening X-ray measurement is considered to involve minimal risk and is necessary to ensure reliable safety measures before the treatment with a biologic.

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

8.5 Other assessments

The other assessments planned for the study are:

- Quality of life questionnaires/patient reported outcomes (PROs)
- [redacted]

8.5.1 Health-related quality of life

The impact of PsA on various aspects of patients' HRQoL will be assessed using the following validated instruments:

- Health assessment questionnaire – disability index (HAQ-DI©) (see Section 8.3.1)
- [redacted]
- [redacted]
- Psoriatic Arthritis Quality of Life (PsAQoL)
- Functional assessment of chronic illness therapy© – Fatigue (FACIT©-Fatigue)
- Dermatology life quality index (DLQI)

All questionnaires will be available, where possible, in the local languages of the participating countries and should be completed by patients before they see the study physician. All

questionnaires will be completed at the defined visits / time points listed in Table 8-1 and prior to the patient seeing the investigator for any clinical assessment or evaluation. The questionnaires will be in the respondent's local language. The patient should be given sufficient instruction, space, time and privacy to complete the questionnaires. The study coordinator should check the questionnaires for completeness and encourage the patient to complete any missing responses. Completed questionnaires should be reviewed and assessed by the investigator, before the clinical examination, for responses which may indicate potential AEs or SAEs. This assessment should be documented in the source records. If AEs or SAEs are confirmed, the investigator should record the events as per instructions given in Section 10.

Guidelines for administering the PRO questionnaires can be found in Appendix 2.

[redacted]

8.5.1.3 Psoriatic Arthritis Quality of Life

The PsAQoL (McKenna et al 2004) is a self-administered, 20-item questionnaire to evaluate the effect of PsA on a patient's quality of life. This easy-to-complete instrument contains 20

statements, which have to be marked by the responder whether they apply to them at the moment or not (true/not true). The results reflect the patient's actual condition. The maximum score is 20; lower scores refer to better HRQoL.

8.5.1.4 Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue©)

The FACIT-Fatigue© (Cella et al 1993; Yellen et al 1997) is a 13-item questionnaire that assesses self-reported fatigue and its impact on daily activities and function.

The purpose of FACIT-Fatigue© in this study is to assess the impact of fatigue on patients with PsA.

8.5.1.5 Dermatology Life Quality Index

The DLQI (Finlay and Khan 1994) is a 10-item general dermatology disability index designed to assess HRQoL in adult patients with skin diseases such as eczema, psoriasis, acne and viral warts. The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment and work/school. The measure is widely used: it has been tested across 32 different skin conditions and is available in multiple languages. The recall period is the past 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 HRQoL impairment. Additionally, each subscale of the DLQI may be analyzed separately.

[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/reference 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 by patient/guardian
- Pregnancy
- Any severe or serious AE that requires treatment with an unacceptable co-medication
- Any situation in which study participation might result in a safety risk to the patient
- AEs, abnormal laboratory values or abnormal test results that indicate a safety risk to the patient
- 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 7).
- Any other protocol deviation that results in a significant risk to the patient's safety

In addition to these requirements for study treatment discontinuation, the investigator should discontinue study treatment for a given patient if there is a lack of improvement or worsening

of their symptoms, or if on balance, the investigator believes that continuation would be detrimental to the patient's well-being.

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.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (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
- AEs/SAEs

For patients who discontinue study treatment, a Dosage Administration Record eCRF should be completed, giving the date and primary reason for stopping study treatment.

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

9.1.2 Withdrawal of informed consent

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/reference 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 for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible (provide instruction for contacting the patient, when the patient should stop taking drug, when the patient should come for a final visit) 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 sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol i.e. Follow-up visit (week 36). Information on the patient's completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the appropriate Study Phase Completion in the eCRF.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study as deemed appropriate by the investigator. Based on the individual risk/benefit profile of a patient, treatment options may include DMARDs.

In case of follow-up medical care with a biologic treatment the waiting period before initiating treatment will be at the discretion of the investigator or a minimum of 5 half-lives of the selected biologic treatment, whichever is longer.

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. In addition, all reports of intentional misuse and abuse of the study treatment are also considered as an AE irrespective of a clinical trial event has occurred. See Section 10.1.5 for an overview of the reporting requirements.

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 and other investigational treatment. 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 a lack of efficacy or progression of underlying illness are not caused by the trial drug, 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 study treatment or other 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 (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

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

Adverse events (including lab 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 12 weeks (secukinumab) or 20 weeks (ustekinumab) 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. 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 medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification (IN) or an aggregate safety finding. New information might require an update to the informed consent and has then to be discussed with the patient.

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. Alert ranges for laboratory and other test abnormalities are included in Appendix 7.

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.

10.1.3 SAE reporting

Randomized patients

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until Week 36 (12 weeks (secukinumab) or 20 weeks (ustekinumab) after the last dose of study treatment) 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.

Screen failures

SAEs 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.

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a 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 24-week follow-up period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

Treatment-emergent elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded), study drug should be discontinued immediately, patient should be hospitalized, if clinically appropriate, and causality needs to be established. Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

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 and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up (birth, 1, 3, and 12 months after the expected delivery) should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes (birth, 1, 3, and 12 months after the expected delivery) 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.

10.1.5 Reporting of study treatment errors including misuse/abuse

Study treatment errors are unintentional errors in the prescribing, dispensing, and administration of study treatment.

Study treatment misuse refers to situations where the study treatment is intentionally and inappropriately used not in accordance with the protocol.

Study treatment abuse corresponds to the persistent or sporadic, intentional excessive use of study treatment, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol, including misuse or abuse, must be reported on the AE (or SAE, if the event meets the definition of an SAE) CRF.

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 patients 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. For further information on notable laboratory values, see Appendix 7.

10.2.2 Renal safety monitoring

To date, there has been no safety signal for nephrotoxicity with secukinumab in over 12,000 patients and healthy patients 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 resulting in clinically significant abnormal values (see Appendix 7 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 (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

11 Data collection and database management

11.1 Data collection

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

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been 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 electronic data capture (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.

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 (ATC) classification system. Medical history/current medical conditions and AEs will be coded using the medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about all study treatment(s) dispensed to the patient and all dosage changes will be tracked.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

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 Good Clinical Practice, the

progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/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 data base lock for the trial. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The primary analyses for all efficacy and safety endpoints will be carried out after the last patient completed Week 28 assessment.

12.1 Analysis sets

The Randomized Analysis Set (RAS) consists of all randomized patients. Unless otherwise specified, miss-randomized patients will be excluded from the RAS.

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

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

12.2 Patient demographics and other Baseline characteristics

Demographic and other Baseline data including disease characteristics will be listed and summarized descriptively by treatment group 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, preferred term 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, 25th and 75th percentiles, 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 prior to and after the start of the study treatment will be listed and summarized according to the 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 of the study. 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 achieving at least one treatment of a particular ATC.

12.4 Analysis of the primary endpoint(s)

The primary aim of the study is to demonstrate that secukinumab 300mg is superior to ustekinumab 45mg/90mg in terms of achieving a HAQ-DI® response ≥ 0.35 in change from baseline to week 28 in adult patients with psoriatic arthritis, who failed previous TNFα inhibitor treatment.

12.4.1 Definition of primary endpoint(s)

The primary endpoint variable is the proportion of patients achieving treatment response as defined by a change in HAQ-DI® ≥ 0.35 from baseline to week 28.

The analysis of the primary variable will be based on the treatment-policy estimand:

- Analysis set: FAS,
- Variable of interest: proportion of patients achieving treatment response as defined by a change in HAQ-DI® ≥ 0.35 from baseline to week 28,
- Intervention effect: effect between secukinumab 300mg vs. ustekinumab 45mg/90mg regardless of adherence to randomized treatment,
- Summary measure: Odds ratio (OR).

12.4.2 Statistical model, hypothesis, and method of analysis

Initially, statistics were planned as described below. However, due to recruitment issues of study CAIN457FDE04 („AgAIN"), screening has been discontinued as of 31 Jan 2024. Patients who were successfully screened through 31 Jan 2024 were all allowed to be randomized and could complete the study. A total of 119 patients were randomized, which led to 59 patients in one arm and 60 patients in the other arm – herein not further specified due to ongoing blinding. The resulting power under previous assumptions will be approximately 55%. Therefore, only a descriptive analysis will be performed, as inferential analyses would be underpowered (no formal tests will be performed). Missing data for HAQ-DI® response and other binary efficacy endpoints (e.g. response of PASI 90, PASI 100, PsAQoL, etc.) for data up to Week 28 will be replaced once by last-observation-carried forward (LOCF) or as non-responders in the sense of worst-case analysis.

The statistical hypothesis to be tested is that there is no difference in the proportion of subjects fulfilling the HAQ-DI® responder definition at Week 28 between the two treatment arms in the FAS population.

Let p_j denote the proportion of HAQ-DI® responders at Week 28 for treatment group j, j = 0,1, where

- 0 corresponds to the ustekinumab 45mg/90mg treatment arm,
- 1 corresponds to the secukinumab 300mg arm.

The following hypotheses will be tested:

H_0: $(p_1 / (1-p_1)) / (p_0 / (1-p_0)) = 1$ vs. H_A: $(p_1 / (1-p_1)) / (p_0 / (1-p_0)) \neq 1$

In other words:

H_A: The odds ratio of achieving a HAQ-DI® response at Week 28 for the comparison of secukinumab 300mg vs. ustekinumab 45mg/90mg is different from 1.

The primary endpoint of HAQ-DI® response at Week 28 will be analyzed via a multiple logistic regression model with treatment and randomization strata as factors and baseline HAQ-DI® score as a covariate. Odds ratios will be computed for comparisons of secukinumab versus ustekinumab regimen utilizing the logistic model fitted to the data. Superiority in favor of secukinumab for the primary efficacy variable will be claimed if the two-sided p-value for the factor treatment is ≤ 0.05.

12.4.3 Handling of missing values/censoring/discontinuations

Missing data for HAQ-DI® response and other binary efficacy endpoints (e.g. response of PASI 90, PASI 100, PsAQoL etc.) for data up to Week 28 will be handled by Multiple Imputation (MI) utilizing all accumulated patient data irrespective of on- or off-treatment. All considered endpoints should be imputed separately.

Multiple Imputation (MI) is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Within this analysis the composites of e.g. the ACR or the

HAQ-DI® score will be imputed and response variables will be derived based on the imputed scores. In the multiple imputation analysis the response status will be imputed based on the individual treatment arm information.

Patients who were unblinded prior to the scheduled time point will be considered non-responders from the time of unblinding up to Week 28.

Continuous variables (e.g. VAS of patient's assessment of pain) up to Week 28 will be analyzed by means of a mixed-effect model for repeated measures (MMRM), which is valid under the missing at random (MAR) assumption. Missing data for continuous efficacy endpoints due to missed or skipped visits will therefore not be applicable to multiple imputation. Analysis visits up to Week 28 will be analyzed in this fashion.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses and supportive analyses will be conducted in order to provide evidence that the results seen from the primary analysis are robust. These analyses will center on the deviations in model assumptions, and the treatment of missing data.

Supportive analyses

Supportive analyses to be conducted are primarily related to investigating possible subgroup-by-treatment interaction effects for the following subgroups:

- Age (≤ 65 vs. > 65)
- Gender (male vs. female)
- Number of previous TNFα treatment regimens (≤ 2 vs. > 2)

12.5 Analysis of secondary endpoints

The analyses of secondary endpoints will be performed when all patients have completed the Week 28 assessment. For evaluation of secondary efficacy outcomes, no formal statistical testing procedure will be applied.

12.5.1 Efficacy endpoint(s)

Binary secondary efficacy endpoints like the proportion of patients with a PASI 90 response or Minimal Disease Activity at Week 28 will be evaluated using the same multiple logistic regression model utilized for the primary efficacy endpoint with treatment and randomization stratum as factors and the respective baseline score value, if applicable, as a covariate.

For continuous endpoint variables like the patient's assessment of pain (VAS) or tender and swollen joint count, the between-treatment difference in change from baseline will be evaluated using a MMRM. Treatment group, randomization stratum and analysis visit will be included as factors in the models. Additionally, each respective baseline score value of the endpoint variable will be included as a covariate. Treatment group by analysis visit and baseline score by analysis visit will be included as interaction terms in the model. An unstructured covariance matrix will be assumed. The treatment effect for the secukinumab 300 mg regimen at different analysis visits will be determined from the pairwise comparison performed between the two treatment groups.

12.5.2 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) 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 death 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 (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

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 (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term

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

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any AE, having any AE in each primary system organ class and having each individual AE (PT). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a patient reported more than one AE with the same PT; the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable. Serious adverse events will also be summarized.

Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment 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/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare Baseline to the worst on-treatment value.

12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

As mentioned in Section 12.4.2, recruitment of the study was stopped on 31 Jan 2024 and only 119 patients could be randomized. The resulting power under previous assumptions will therefore be ~55%, and only a descriptive analysis will be performed.

12.8.1 Primary endpoint(s)

Calculation of the sample size was based on the primary efficacy response, HAQ-DI® at Week 28, for a comparison of secukinumab 300 mg vs. ustekinumab 45 mg / 90 mg in TNFα-IR PsA patients utilizing the FAS. Available data from the FUTURE5 trial within the TNFα-IR subpopulation showed a HAQ-DI® response of secukinumab 300 mg of 57.6% and 56.1% at Weeks 28 and 32, respectively (Non-Responder Imputation). Conservatively, assuming a HAQ-DI® response of at least 57% at Week 28 seems therefore justifiable for secukinumab 300 mg.

Following results from the PSUMMIT2 trial of ustekinumab 45 mg / 90 mg, the proportion of HAQ-DI® responders at Week 24 was 36.1%.
With a HAQ-DI® response of 57% in the secukinumab 300 mg arm and a 36.1% response in the ustekinumab 45 mg / 90 mg arm at Week 28 (corresponding to an odds ratio of 2.35), 140 patients per treatment arm are required to achieve a power of > 90% in order to demonstrate superiority at a significance level of 0.05 using the two group continuity corrected χ^2-test of

equal proportions. In order to account for some uncertainties in the underlying assumptions and to compensate for some expected drop-out, a total of 310 patients (155 in the secukinumab 300 mg and 155 in the ustekinumab 45 mg / 90 mg arm) should be randomized into the study.

Furthermore, this number of patients will allow a power of around 90% in order to claim a significant benefit of secukinumab 300 mg vs. ustekinumab 45 mg / 90 mg in TNFα-IR PsA patients, using the PASI 90 responder definition. Available data from the FUTURE5 trial within the TNFα-IR subpopulation showed a PASI 90 response of secukinumab 300 mg of 62.9% and 57.1% at Weeks 24 and 32, respectively (Non-Responder Imputation). Conservatively, assuming a PASI 90 response of at least 57.1% at Week 28 seems therefore justifiable for secukinumab 300 mg. Following results from the PSUMMIT2 trial of ustekinumab 45 mg / 90 mg, the proportion of PASI 90 responders at Week 24 was 37.3% and remained stable over time.

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 GCP, 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, the investigator/institution 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 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.

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16 Appendices

16.1 Appendix 1: Classification criteria for psoriatic arthritis (CASPAR)

To meet the Classification of Psoriatic Arthritis (CASPAR) criteria for diagnosis of psoriatic arthritis (Taylor et al 2006), a subject must have inflammatory articular disease (joint, spine or entheseal) and at least 3 points from the following 5 categories:

- Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis
  - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.* (**2 points**)
  - A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider. (**1 point**)
  - A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report. (**1 point**)
- Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination (**1 point**)
- A negative test result for the presence of rheumatoid factor by any method except latex (**1 point**)
- Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist (**1 point**)
- Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot (**1 point**)

Total score:

(The CASPAR criteria eCRF will autopopulate the total number of points of the CASPAR criteria met by the subject. If the total score ≥ 3, the subject meets CASPAR criteria for PsA diagnosis.)

* Current psoriasis is assigned a score of 2; all other features are assigned a score of 1

16.2 Appendix 2: Guidelines for administering the questionnaires for patient reported outcomes

Before trial start

Study coordinators should familiarize themselves with the PRO questionnaire(s) in the trial and identify any items where a patient's response might highlight issues of potential concern.

[redacted]

Before completion

Subjects should be provided with the correct questionnaire at the appropriate visits and in the appropriate language.

Subjects should have adequate space and time to complete the forms.

Patients should be provided with a firm writing surface (such as a table or a clip board).

Questionnaire should be administered before the clinical examination.

During completion

Administrator may clarify the questions but should not influence the response.

Only one response for each question.

Also see "Addressing Problems and Concerns".

After completion

Check for completeness and not for content*

Data should be sent from the eCRF / electronic device.

Data should be reviewed by Investigator for AEs.

*However, any response which may directly impact or reflect the patient's medical condition (e.g. noting of depression) should be communicated by the study coordinator to the investigator).

Addressing Problems and Concerns

Occasionally a patient may have concerns or questions about the questionnaires administered. Guidance related to some of the most common concerns and questions are given below.

The patient does not want to complete the questionnaire(s)

Tell the patient that completion of the questionnaire(s) is voluntary. The goal is to better understand the physical, mental and social health problems of patients. Emphasize that such information is as important as any other medical information and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the

respondent has filled in the past. If the patient still declines, retrieve the questionnaires. Record the reason for the decline and thank the patient.

The patient is too ill or weak to complete the questionnaire(s)

In these instances, the coordinator may obtain patient responses by reading out loud each question, followed by the corresponding response categories, and entering the patient's response. No help should be provided to the patient by any person other than the designated study coordinator. The coordinator should not influence patient responses. The study coordinator cannot translate the question into simpler language and has to be read verbatim.

The patient wants someone else to complete the questionnaire(s)

In no case should the coordinator or anyone other than the patient provide responses to the questions. Unless specified in the study protocol, proxy data are *not* an acceptable substitute for patient self-report. Patients should be discouraged from asking a family member or friend for help in completing a questionnaire.

The patient does not want to finish completing the questionnaire(s)

If non-completion is a result of the patient having trouble understanding particular items, ask the patient to explain the difficulty. Re-read the question for them *verbatim* but do not rephrase the question. If the respondent is still unable to complete the questionnaire, accept it as incomplete. Thank the patient.

The patient is concerned that someone will look at his/her responses

Emphasize that all responses are to be kept confidential. Point out that their names do not appear anywhere on the questionnaire, so that their results will be linked with an ID number and not their name. Tell the patient that his/her answers will be pooled with other patients' answers and that they will be analyzed as a group rather than as individuals. Tell the patient that completed forms are not routinely shared with treating staff and that their responses will only be seen by you (to check for completeness) and by the investigator. Any response which may directly impact on or reflect their medical condition (*e.g.* noting of severe depression) will be communicated by the coordinator to the physician.

The patient asks the meaning of a question/item

While completing the questionnaire, some patients might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the patient by rereading the question for them *verbatim.* If the patient asks to interpret the meaning of an item, do not try to explain it, but suggest that he/she use his/her own interpretation of the question. Patients should answer the questions based on what *they* think the questions mean.

A General Information about all questionnaire(s):

All questionnaires have to be completed by the patients in their local languages using an electronic device. The questionnaires should be completed by the patients in a quiet area free from disturbance, and before any visit assessments. Patients should receive no help from family members; if questions cannot be answered alone (due to problems with reading or understanding), then the doctor or nurse should read the questions and record the patient's responses without influencing their answers. The information provided is strictly confidential

and will be treated as such. If a patient has missed a question or given more than one response per question, then this should be brought to patient. Incomplete questions should not be accepted without first encouraging the patient to complete unanswered questions.

The investigator must complete the patient/visit information and ensure that the center number, patient's number and initials are identical to the CRF. As there are no source data for this questionnaire, the data queries will be restricted to patient/visit information.

16.3 Appendix 3: American College of Rheumatology (ACR) Measures and Criteria of Response

Number of tender joints

Sixty-eight joints (68) are scored as either tender or not tender: 8 distal interphalangeal, 10 proximal interphalangeal and 10 metacarpophalangeal joints of the hands, the 10 metatarsophalangeal and 10 proximal interphalangeal joints of the feet, the 2 wrists, 2 elbows, 2 shoulders, 2 acromioclavicular, 2 sternoclavicular, 2 temporomandibular, 2 hips, 2 knees, 2 talo-tibial, and 2 mid-tarsal joints.

Joint tenderness is to be scored present (1) or absent (0).

Number of swollen joints

Joints are to be scored as either swollen (1) or not swollen (0). The 66 joints to be examined for swelling are the same as those examined for tenderness, however excluding both hip joints.

Patient's assessment of PsA pain

On a 100 mm non-anchored visual analog scale, from no pain to unbearable pain.

Patient's global assessment of disease activity

On a 100 mm non-anchored visual analog scale, from no arthritis activity to maximal arthritis activity, after the question "Considering all the ways your arthritis affects you, draw a line on the scale for how well you are doing".

[redacted]

Patient's assessment of physical function

Health Assessment Questionnaire – HAQ-DI©

[redacted]

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- [redacted]

[redacted]

16.4 Appendix 4: Standard reference table for the LDI

Table 16-1 LDI reference table for hands (in cm)

Digit	Men	Women
Thumb	7.0	5.8
Index	6.3	5.4
Middle	6.3	5.4
Ring	5.9	5.0
Little	5.2	4.4

Table 16-2 LDI reference table for feet (in cm)

Digit	Men	Women
Central toe	8.2	7.2
Second	5.2	4.6
Middle	5.0	4.4
Fourth	5.0	4.4
Little	5.2	4.5

16.5 Appendix 5: The Psoriasis Area and Severity Index (PASI)

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of disease is calculated as follows. In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20% and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and desquamation (scaling), which are each rated on a scale of 0 to 4. The scoring system for the signs of the disease (erythema, induration, and desquamation (scaling)) are:

0 = none; 1= slight; 2 = moderate; 3 = severe; and 4 = very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

0 = no involvement

1 = 1% to 9% involvement

2 = 10% to 29% involvement

3 = 30% to 49% involvement

4 = 50% to 69% involvement

5 = 70% to 89% involvement

6 = 90% to 100% involvement

To help with the area assessments, the following conventions should be noted:

- the neck is considered part of the head
- the axillae and groin are part of the trunk
- the buttocks are part of the lower extremities

The PASI formula is: PASI = 0.1 (Eh + Ih + Dh) Ah + 0.3 (Et +It+ Dt) At+ 0.2 (Eu + Iu + Du) Au+ 0.4 (El +II+ Dl) AI (where E= erythema, I = induration, D = desquamation and A = area)

Table 16-3 PASI Scoring Worksheet

	Head	Upper extremities	Trunk	Lower extremities
Redness †				
Thickness †				
Scale †				
Sum of rows 1, 2, and 3				
Area score ‡				
Score of row 4 x row 5 x the area multiplier	Row 4 x row 5 x 0.1	Row 4 x row 5 x 0.2	Row 4 x row 5 x 0.3	Row 4 x row 5 x 0.4
Sum row 6 for each column for PASI score				

a. Divide body into four areas: head, arms, trunk to groin, and legs to top of buttocks.

b. Generate an average score for the erythema, thickness, and scale for each of the 4 areas (0=clear, 1-4=increasing severity).

c. Sum scores of erythema, thickness, and scale for each of the 4 area.

d. Generate a percentage for skin covered with psoriasis for each area and convert that to a 0-6 scale. ‡

e. Multiply score of item c above times item d above for each area and multiply that by 0.1, 0.2, 0.3 and 0.4 for head, arms, trunk, and legs, respectively.

f. Add these scores to get the PASI score.

† Erythema, thickness, and scale are measured on a 0-4 scale (none, slight, mild, moderate, severe)

‡ Area scoring criteria (score: % involvement).

0: 0% (clear)
1: <10%
2: 10-<30%
3: 30-<50%
4: 50-<70%
5: 70-<90%
6: 90-100%

Derived from Feldman SR, Krueger GG (2005). Psoriasis assessment tool in clinical trials. Ann Rheum Dis; 64 (Suppl 2);ii65-8.

16.6 Appendix 6: Liver event and laboratory trigger definitions and follow-up requirements

Table 16-4 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers	3 x ULN < ALT / AST ≤ 5 x ULN 1.5 x ULN < TBL ≤ 2 x ULN
Liver events	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST > 3 × ULN and INR > 1.5
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any adverse event potentially indicative of a liver toxicity *

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

TBL: total bilirubin; ULN: upper limit of normal

Table 16-5 Follow-up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for *more than 2 weeks*, discontinue the study drug Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	Repeat LFT within 48 hours If elevation persists, establish causality Complete liver eCRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study drug immediately Hospitalize the patient Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	Consider study drug interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete liver eCRF	Investigator discretion

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

TBL: total bilirubin; ULN: upper limit of normal

[a] Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

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

[c] Resolution is defined as an outcome of one of the following: (1) return to Baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

16.7 Appendix 7: Clinically notable laboratory values

- The following guidance will be used to define expanded limits and notable abnormalities of key laboratory outcomes.
- Clinically notable values will be forwarded to Novartis in the same time as sent to the investigators. Any intervention based on these laboratory values should be discussed with Novartis personnel.

Table 16-6 Clinically notable laboratory values

Laboratory variable	Notable criteria
Liver function and related variables	
SGOT (AST)	>3 x ULN
SGPT (ALT)	>3 x ULN
Bilirubin	>2 x ULN
Alkaline phosphatase	>2.5 x ULN
Renal function, metabolic and electrolyte variables	
Creatinine (serum)	>2 x ULN
Hematology variables	
Hemoglobin	20 g/L decrease from Baseline
Platelet count	<100 x 10^9/L
White blood cell count	<0.8 x LLN
Neutrophils	<0.9 x LLN