NOVARTIS

Global Clinical Development - General Medicine

AIN457/Secukinumab

Clinical Trial Protocol (CAIN457F2354)

A 52-week, multicenter study to assess the time course of response to secukinumab on joint inflammation using Power Doppler ultrasonography in patients with active psoriatic arthritis

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
anti-CCP	Anti Cyclic Citrullinated Peptide
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
BSA	Body Surface Area
β-hCG	Beta Human Chorionic Gonadotropin
CASPAR	Classification Criteria for Psoriatic Arthritis
CHMP	Committee for Medicinal Products for Human Use
CRF	Case Report Form
COX-1	Cyclo-oxygenase-1
COX-2	Cyclo-oxygenase-2
CPO	Country Pharma Organization
CRO	Contract Research Organization
CRP	C-Reactive Protein
DAR	Dose Administration Record
DOH	Declaration of Helsinki
DMARD	Disease Modifying Anti-Rheumatic Drug
DS&E	Drug Safety & Epidemiology
DSUR	Developmental Safety Update Report
eCRF	Electronic Case Report Form
EEA	European Economic Area
EMEA	European Medicines Agency
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLOESS	Global OMERACT-EULAR Synovitis Score
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI©	Health Assessment Questionnaire-Disability Index
HCG	Human Chorionic Gonadotropin
hsCRP	High Sensitivity C-Reactive Protein

IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
IL-17	Interleukin 17
IR	Inadequate Response
IRB	Institutional Review Board
IRT	Interactive Response Technology
JE	Joint Effusion
MAR	Missing at Random
MCP	Metacarpophalangeal
MDA	Minimal Disease Activity
METc	Medical Ethics Committee
MHLW	Ministry of Health, Labor and Welfare
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measures Model
MRI	Magnetic Resonance Imaging
MTP	Metatarsophalangeal
MTX	Methotrexate
OC/RDC	Oracle Clinical/Remote Data Capture
OMERACT	Outcome Measures in Rheumatology
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PDUS	Power Doppler Ultrasonography
PFS	Pre-Filled Syringes
PGA	Physician's Global Assessment
PIP	Proximal Interphalangeal
PPD	Purified Protein Derivative
PsA	Psoriatic Arthritis
PUVA	Psoralen and Ultraviolet A
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
SAE	Serious Adverse Event
s.c.	Subcutaneous

SF36	Short Form Health Survey
SH	Synovial Hyperplasia
SIB	Suicidal Ideation and Behavior
SJC	Swollen Joint Count
SpA	Spondyloarthritides
SPARCC	Spondyloarthritis Research Consortium of Canada
SSR	Sample size re-estimation
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor
TNFα	Tumor Necrosis Factor Alpha
US	Ultrasound
UVA	Ultraviolet A
UVB	Ultraviolet B
VAS	Visual Analog Scale
WMA	World Medical Association

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the study.
DMARD	Disease modifying anti-rheumatic drug; in this study this term refers only to non-biologics.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Medication number	A unique identifier on the label of each study drug package in studies that dispense medication using an interactive response technology (IRT) system.
Mis-randomization	A patient who is randomized to a treatment group, but did not receive any study treatment.
Clinical non-responder	A patient with < 20% improvement from Baseline in either tender joint count (TJC) or swollen joint count (SJC).
Period	The planned stage of the patient's participation in the study. Each period serves a purpose in the study as a whole. In this study, there is a Screening period for determination of patient eligibility, Period 1, which is a 12-week double-blind placebo-controlled period; Period 2, which is 12-week open-label maintenance period and Period 3, which is 6-month open label extension period.
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.
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment.
Re-screening	A patient who qualified for all or most eligibility criteria but could not be randomized within the Screening period can be considered for re-screening only once.
Rescue medication	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.
Clinical responder	A patient with ≥ 20% improvement from Baseline in both TJC and SJC.
Study drug/treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug(s), active drug run-ins or background therapy.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal.
Patient number	A number assigned to each patient who enrolls into the study.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study.
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data.

Amendment 1

Amendment rationale

This protocol amendment is issued for the following reasons:

- For those countries where it is required, add hepatitis B, hepatitis C and human immunodeficiency virus (HIV) serology testing during the Screening Period to the assessment schedule (Table 6-1). These tests were already outlined in Exclusion Criterion No. 21 and results of these tests determine eligibility for the study. Thus the addition to the assessment schedule in this amendment is made in order to clarify and remove inconsistencies in the protocol.
- To add collection of Spondyloarthritis Research Consortium of Canada (SPARCC) at the Screening Visit to the assessment schedule as it was previously omitted in error for this visit (Table 6-1). This test was already outlined in Inclusion Criterion No.5 and results of this test determine eligibility for the study. Thus the addition to the assessment schedule in this amendment is made in order to clarify and remove inconsistencies in the protocol.
- To remove one reference to a placebo injection in Treatment Period 2 that was included in error. No placebo injection is administered in Treatment Period 2 as it is open label.
- To document that the total time required for each PDUS assessment (either in the main study or substudy) will be recorded in the eCRF and to add 2 exploratory endpoints (one for the main study and one for the sub-study) regarding the time spent on PDUS assessments.
- To document that the name and type of PDUS machine used will be recorded in the eCRF.
- To updated background information with respect to the most recent Developmental Safety Update Report (DSUR).

Changes to the protocol

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

- Section 3.6: Revised statement based on updated DSUR as follows:

  From*: "As of 12-Jul-2014 (safety cut-off for latest IB and Developmental Safety Update Report (DSUR), approximately 10 900 healthy subjects and patients have been enrolled into the secukinumab clinical program and in trials where secukinumab has been used as a protocol-specified treatment, of whom approximately 8 600 healthy subjects and patients have received at least one dose of secukinumab in Novartis-sponsored clinical trials."*

  To: "*As of **25-Jun-2015** (safety cut-off for latest Developmental Safety Update Report (DSUR), approximately **12000 subjects** (which included patients and a small number of healthy volunteers) have been enrolled into the secukinumab clinical program (including trials where secukinumab has been used as a protocol specified treatment), of which approximately **9600 subjects** (comprising of patients and healthy volunteers) have received at least one dose of secukinumab."*

- Section 5.2.2: Deletion of the wording "*and placebo (1.0 mL PFS)*" for Period 2.

- Section 6, Table 6-1: Addition of row with wording "*hepatitis B, C and HIV serology testing (only in countries where required)***" at the Screening Visit, along with footnote "*** Hepatitis B and/or hepatitis C and/or HIV serology testing to be performed during screening period only if required as per local medical practice or local regulations prior to initiation of therapy. These assessments will be documented in source records only and will not be entered into the eCRF."*
- Section 6, Table 6-1: Addition of SPARCC assessment at the Screening Visit.
- Section 6.2: Addition of the wording "*The SPARCC will be assessed at both the Screening and Baseline Visit*."
- Section 6.4.1: Addition of the wording "*The total time required for each PDUS assessment in the study will be recorded in the eCRF*" and

  "*The name and type of PDUS machine used will also be recorded in the eCRF. PDUS equipment recommendations are described in Appendix 9*."
- Section 6.4.1.1: Addition of the wording "*the total time required for each PDUS assessment in the sub-study will be recorded in the eCRF*," and

  "*The name and type of PDUS machine used will also be recorded in the eCRF. PDUS equipment recommendations are described in Appendix 9*."
- Section 7.4: Revised statement based on updated DSUR as follows:
  From: *"There has been no safety signal for nephrotoxicity with secukinumab to date in over 8 600 patients and healthy subjects exposed (safety cut-off date of 12-Jul-2014, DSUR No. 004), and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney."*
  To: *"There has been no safety signal for nephrotoxicity with secukinumab to date in over* ***9600 patients*** *and healthy subjects exposed (safety cut-off date of* ***25-Jun-2015, DSUR No. 005****), and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney."*
- Section 9.4.2: Addition of the words "*center, machine type*" to the following statement: Between-treatment differences in the change in GLOESS will be evaluated using a mixed-effect model repeated measures model (MMRM) with treatment regimen**,** *center, machine type* and analysis visit as factors and weight and baseline GLOESS as continuous covariates.
- Section 9.5.2: Addition of the words "*center, machine type*" to the following statement: The between treatment differences will be compared by means of a MMRM with treatment regimen, *center, machine type* and analysis visit as factors and baseline weight and baseline score as continuous covariates.
- Section 9.5.3: Addition of the exploratory endpoint: "overall time spent on PDUS assessments of joint inflammation and enthesitis for the main study and breakdown of time spent on these assessments by visit."

[redacted]

At the time this amendment was written no patient had been enrolled in the study.

Amendment 2

Amendment rationale

Study CAIN457F2354 is a phase IIIb, 52-week, multicenter, international study to assess the time course of response to secukinumab on joint inflammation using Power Doppler ultrasonography in patients with active psoriatic arthritis (PsA). The study was started on 22-Aug-2016 (First Patient First Visit). As of 23-Feb-2017, 12 of 19 patients screened at 17 active sites were assessed as screen failures mainly because they did not meet inclusion criterion 4 related to PDUS entry criteria i.e. they did not present with a total synovitis score ≥ 2 and enough inflammation on PD signal ≥ 2 for at least 2 affected joints. Of the remaining 7 patients being screened, 3 were still in screening and 4 patients have been enrolled and randomized into the study as of 23-Feb-2017. Some active sites from across EU have also suggested that a total of 20 study visits was too demanding for patients given most of them continued to work.

The rationale for the amendment is

1. To increase the study feasibility and to ease the study visit burden on patients without compromising the primary and secondary objectives of the study until Week 12 based on the number of screen failures reported to date and feedback received from active centers on the number of study visits.
    - To amend inclusion criterion no. 4, an ultrasound entry criterion that is considered too restrictive as it has resulted in the most screen failures, to allow inclusion of patients with a total synovitis score ≥ 2 and inflammation related to **PD signal ≥ 2 for at least 1 affected joint** as observed via PDUS of 48 joints, OR with an inflammation related to **PD signal ≥ 1** for at least **2 affected joints** as observed via PDUS of 48 joints.
    - To remove the study visits and associated study assessments at Week 28, 32, 40, 44 and 48 from the open-label Extension Period and to introduce home administration of study drug at these time points; to remove the clinical efficacy assessments (including PDUS assessments) from the double-blind Week 3 visit; and to remove the PDUS assessment from the Week 56 follow-up visit. The Extension Period is optional according to Investigator's judgment and patient consent and exploratory study objectives only apply to this period. The removal of study visits during the Extension Period will not compromise patient safety given the benefit/ risk of secukinumab has already been assessed and secukinumab is registered in all participating countries. The removal of the Week 3 efficacy assessments is to decrease the burden of weekly assessments for patients during the initial period of the study without compromising the primary or secondary objectives of the study. Similarly the removal of the follow-up PDUS assessments the Week 56 visit is to decrease the burden of assessments for patients without compromising the study objectives.
2. Clarify different aspects of the protocol following the review of different Ethics Committees (ECs):
    - Clarification in the patient population that subjects must have had an inadequate response to non-biologic DMARDs to be consistent with study rationale and primary objective of the study.

- To amend the use of rescue medication so it is less restrictive throughout the study and notably for the patients randomized to placebo during the first 12 weeks to make it more ethical given the risk of potential flare and existence of alternative therapies.
- To update the following aspects of the protocol:
  - To reference the Medical Research Involving Human Subjects Act in the Netherlands (known as the WMO in Dutch) for the Netherlands.
  - To describe specific reporting of SAEs, SUSARs and safety reports to the Medical Ethics Committee (METc in Dutch) for the Netherlands.
  - To describe the reporting of the end date of the study/early termination of the study to METc for the Netherlands.
  - To reference the latest version of the Declaration of Helsinki.
  - To correct the conversion table for corticosteroids and update source references.
  - To add clinical and ultrasound assessment of the contralateral digit at the same time points to allow a descriptive comparison.

3. To update the risk/benefit section of the protocol based on latest Developmental Safety Update Report (DSUR) for secukinumab (covering reporting period 26-Jun-2015 to 25-Jun-2016).
4. To include new safety sub-section section on the reporting of study treatment errors, including misuse/abuse, and to clarify in the AE reporting section that all reports of intentional misuse and abuse of the product are also considered an AE irrespective if a clinical event.
5. To remove all references to Japan as this study will not be conducted in Japan.
6. To add that a visit window of ± 3 days must be observed for visits with PDUS assessments scheduled from Baseline through to the end of study,
7. To amend the Screening period from “2 to 4 weeks” to “1 to 4 weeks”.
8. To correct typo in Appendix 6 from “22 paired joints” to “24 paired joints”.

Changes in the protocol

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

A summary of the changes that have been made to the protocol is provided below.

The wording of various sub-sections to “Protocol Summary”, “Introduction (Section 1.1.2)”, “Sub-study objectives (Section 2.3.1)”, “Study design (Section 3.1)”, “Rationale of study design” (Section 3.2)”, “Rationale of dose/regimen, route of administration and duration of treatment (Section 3.3)”, “Rationale for choice of comparator (Section 3.4)”, “Risks and benefits (Section 3.6)”, “Inclusion criteria (Section 4.1)”, “Investigational treatment (Section 5.1.1)”, “Systemic corticosteroids, (Table 5-1, Section 5.1.2.3)”, “NSAIDs (including COX-1 or COX-2 inhibitors), low strength opioids and acetaminophen/paracetamol (Section 5.1.2.4)”, “Treatment Arms (Section 5.2)”, “Group 1: secukinumab double-blind followed by secukinumab open-label from Week 12 (Section 5.2.1)”, “Group 2: placebo followed by secukinumab from Week 12 (Section 5.2.2),” “Treatment assignment, randomization (Section 5.3)”, “Dispensing the investigational treatment (Section 5.5.2)”,

"Handling of investigational treatment (Section 5.5.3.1)" "Instructions for prescribing and taking study treatment (Section 5.5.4)", "Rescue medication (Section 5.5.6)", "Concomitant medications (Section 5.5.7)", "Early study termination (Section 5.5.14)", "End of study (Section 5.5.15)", "Visit schedule and assessments (Section 6, Table 6-1 and Table 6-2)", "Treatment exposure and compliance (Section 6.3)", [redacted] "Adverse events (Section 7.1)", "SAEs (Section 7.2)", "Reporting of study treatment errors including misuse/abuse (Section 7.5)", "Safety reporting specific to the Netherlands (Section 7.2.2.1)", "Site monitoring (Section 8.1)", "Substudy (Section 9.5.4)", "Regulatory and ethical compliance (Section 10.1)", "Informed consent procedures (Section 10.2)", "References (Section 12)", "Appendix 6 (Section 13.6)", and "Appendix 8 (Section 13.8)" have been amended to reflect the rationale given above. In addition, "an overview of study drug administration" (Table 6-2) has been added to Section 6 to display the timing of home study drug administrations relative to study center drug administrations.

Review requirements by Independent Ethics Committee and Health Authorities

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

The changes described in this amended protocol require IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 3

Amendment rationale

As of 05-Oct-2018, the study recruitment is still ongoing with a total of 96 enrolled patients from 33 active sites in 15 countries. The recruitment in the trial has been longer than expected with a screen failure rate of 35% since the implementation of substantial Amendment 2. Screen failures are mainly due to ultrasound entry criteria not being met, elevated hepatic liver enzymes, or RF+, criteria for disease activity not being met, and withdrawal of informed consent.

The rationale for the amendment is as follows:

1. To update the sample size calculation in the trial keeping in mind the difficulties of recruitment.

   The primary objective of the study is to demonstrate a difference between secukinumab and placebo in terms of response to joint inflammation over the time course of 12 weeks as measured by Global OMERACT-EULAR Synovitis Score (GLOESS) using Power Doppler Ultrasound (PDUS) as a very sensitive imaging technology in PsA patients with an inadequate response to non-biologic disease-modifying anti-rheumatic drugs (DMARDs). Secukinumab has already proven to be consistently superior to placebo in terms of clinical benefit across the FUTURE 1-5 program, so there is no expectation of inferiority of secukinumab versus placebo in ultrasound outcomes. The efficacy results

will be tested with a 1-sided strategy to maximize sensitivity in the available sample and to overcome recruitment difficulties.

The initial sample size calculation for this trial was extrapolated from an ultrasound study assessed to evaluate the early response of abatacept on synovitis in patients with rheumatoid arthritis (D'Agostino et al 2016) given the lack of a previous ultrasound PsA trial with biologics. A blinded sample size re-estimation was planned in the protocol once the first 60 patients had completed Week 12 and has been supplemented with data from the first 72 patients who reached their Week 12 visit to provide the most accurate estimation. The sample size was re-estimated using the estimated placebo effect of roughly 50% of secukinumab based on data from the FUTURE-2 study (CAIN457F2312) as in the original sample size calculation and adapting the original sample size calculation to be 1-sided with the power relaxed to 80%. The sample size will be adjusted to a new target of 164 patients in total (82 patients per arm). This is mid-way point of the range plus a 5% adjustment based on the observed drop-out rate of patients prior to Week 12 observed at the time of this calculation. The reduction of sample size from 218 to 164 patients will help achieve completion of the last patient first visit by the end of August 2019.

2. To clarify different aspects of the protocol following comments from the Health Authorities (HA), Ethics Committees and investigators.
   a. To clarify the dose of non-steroidal anti-inflammatory drugs (NSAIDs) as rescue therapy prior to assessments in the trial until Week 24. The requirement for patients to return to their previous NSAIDs' dose following a transient increase in dose as rescue therapy 48 hours prior to study assessments was considered unethical by investigators and not accepted by patients who were in pain, and is therefore being removed from the protocol.
   b. To update the entry criteria for the long-term extension period. The entry criteria for the long-term extension phase depend on investigator's judgment on patient clinical benefit and patient's wish given the study drug is registered and commercially available. Patients must sign a separate informed consent form (ICF) to confirm their agreement to participate in the extension period.
   c. To simplify safety requirements, the Adjudication Committee section is being removed as no such committee is required for this study at the current late stage of development.
   d. To clarify the conditions of quality control assessment of the GLOESS scoring performed at the start of the study (for the first patient from each center) and at the end of the study (once the last patient last visit has been completed) in Section 6.4.1 of the protocol in addition to Appendix 6 to be consistent throughout the protocol.
   e. To protect patient data privacy according to latest recommendations from the EEA General Data Protection Regulation (GDPR) requirements, the wording on patient withdrawal of informed consent will be amended to reflect the EEA GDPR requirements.
   f. To add rationale for recording of total time for each PDUS assessment of joint inflammation and enthesitis based on a site audit request. The rationale is to evaluate the variability on time spent by ultrasonographers to assess multiple joints and entheses across the sites.

[redacted]

3. To clarify different aspects of the protocol following clinical trial team review:
   a. To clarify that the 20% improvement in tender joint count (TJC) and swollen joint count (SJC) at Week 24 is relative to Baseline.
   b. To correct figure footnote on use of methotrexate (MTX)/other DMARDs.
   c. To update risk/benefit section based on latest Developmental Safety Update Report (DSUR).
   d. To update renal safety monitoring section based on latest DSUR.
   e. To amend Exclusion Criterion no. 14 to clarify that uncontrolled diabetes is as per investigator's judgment.
   f. To amend wording on NSAID row in table in line with Inclusion Criterion No. 8.
   g. To remove statement on documentation of whether or not a caregiver administered the study treatment in the eCRF as this data is not being collected in this study.
   h. To clarify the timing of the interim and final statistical analyses.
   i. To correct the definition of End of Study.
   j. To include missing sub-section heading on pregnancy and fertility.
   k. To correct details on Interactive Response Technology (IRT) system.
   l. To update list of references.
   m. To define IR on first use and abbreviate throughout the document.
   n. Remove list of authors from title page per latest protocol template.

Changes in the protocol

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

A summary of the changes that have been made to the protocol is provided below:

- List of abbreviations: Updated.
- Glossary of terms: Added definition of personal data and withdrawal of consent.
- Protocol Summary (exclusion criteria): Amended Exclusion Criterion No. 14 to clarify that uncontrolled diabetes is as per the investigator's judgment.
- Section 1.1.3 (power doppler ultrasonography for monitoring treatment response): Added cross reference to Section 6.4.1.
- Section 3.1 (study design), Section 3.4 (rationale for choice of comparator), Section 5.1.2.4 (NSAIDs [including COX-1 or COX-2 inhibitors], low strength opioids and acetaminophen/paracetamol) Section 5.5.6 (rescue medication), Section 5.5.7 (concomitant treatment), and Section 5.5.8 (prohibited treatment): Deleted wording on requirement for patients to return to their previous NSAIDs' dose following a transient increase in dose as rescue therapy 48 hours prior to study assessments.

- Section 3.1 (study design), Section 3.2 (rationale of study design): Amended wording on the long-term extension phase given the study drug is commercially available and registered.
- Section 3.1 (study design), Section 3.2 (rationale of study design), Section 6 (visit schedule and assessments): Added wording to clarify that the extension period is from Week 24 to Week 52 and follow-up period from Week 52 to Week 64. Also added footnote in Table 6-1 to clarify that patients would not be treated at Week 24 unless they signed the ICF for the extension period of the study.
- Section 3.1 (study design), Section 5.2.1 (Group 1: secukinumab double-blind followed by secukinumab open-label from Week 12) and Section 5.2.2 (Group 2: placebo followed by secukinumab from Week 12): Amended wording to clarify that the 20% improvement in TJC and SJC at Week 24 is relative to Baseline.
- Section 3.1 (study design): Corrected footnote on use of MTX/other DMARDs in Figure 3-1.
- Section 3.1 (study design), Section 3.5 (interim analyses/design adaptations), Section 5.4 (treatment blinding), Section 9.6 (interim analyses): Amended statements to clarify that the timing of the final database lock and final statistical analysis.
- Section 3.5 (interim analyses/design adaptations) and Section 9.6 (interim analyses): Removed stop-go decision rules.
- Section 3.6 (risks and benefits): Updated section based on the latest Developmental Safety Update Report for secukinumab.
- Section 4 (population): Reduced planned number of randomized patients from 218 patients (109 per arm) to 164 patients (82 per arm).
- Section 4.2 (exclusion criteria): Amended exclusion criterion no. 14 to clarify that uncontrolled diabetes is as per the investigator's judgment.
- Section 5.5.4 (instructions for prescribing and taking study treatment): Deleted wording to clarify that documentation of whether or not a caregiver administered the study treatment is not required.
- Section 5.5.8 (prohibited treatment): Amended wording on NSAID row in Table 5-2 so it is aligned with Inclusion Criterion No. 8.
- Section 5.5.9 (discontinuation of study treatment): Amended wording to clarify the timing of end of study and follow-up visit assessments for early withdrawal patients.
- Section 5.5.10 (withdrawal of informed consent): Amended section on withdrawal of informed consent to reflect the EEA GDPR requirements.
- Section 5.5.15 (end of study): Amended statement to clarify timing of end of study.
- Section 6.4.1 (power doppler ultrasonography) and Appendix 6 (OMERACT-EULAR Global PDUS OMERACT out of 48 joints): Added wording to clarify the requirements for quality checks of PDUS assessments. In addition, added rationale for recording of total time for each PDUS assessment of joint inflammation and enthesitis.
- [redacted]

- Section 6.5.5.4 (pregnancy and assessments of fertility): Added sub-section heading that was missing in error from previous protocol.
- Section 7.4 (renal safety monitoring): Updated background information on renal safety monitoring.
- Section 8.3 (database management and quality control): Updated details on IRT system.
- Section 8.6 (adjudication committee) and Section 9.5.5 (safety variables): Deleted Section 8.6 and removed statement on adjudication from Section 9.5.5 as no such committee is required for this study.
- Section 9 (data analysis): Amended 2-sided p-values to 1-sided p-values.
- Section 9.5.1 (key secondary efficacy variables): Amended 2-sided hypothesis analyses to 1-sided hypothesis analyses.
- Section 9.6 (interim analyses): Revised details on the blinded sample size re-estimation.
- Section 9.7 (sample size calculation): Amended the sample size from 218 patients (109 per arm) to 164 patients (82 per arm), amended the power of the sample size from 90% to 80% and amended the statistical test for the primary endpoint from a 2-sided to a 1-sided test. In addition, amended the statistical test for other endpoints from a 2-sided to a 1-sided test. Also, removed the wording “treatment difference to placebo of 5.8 will remain as originally planned” as the pooled change will now be used to determine the difference between the treatment and placebo effect.
- Section 12: updated list of references.

Review requirements by Independent Ethics Committee and Health Authorities

- A copy of this amended protocol will be sent to the Independent Ethics Committee (IECs) and Health Authorities.
- The changes described in this amended protocol require IEC approval prior to implementation.
- The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CAIN457F2354
Title	A 52-week, multicenter study to assess the time course of response to secukinumab on joint inflammation using Power Doppler ultrasonography in patients with active psoriatic arthritis.
Brief title	Study of application of Power Doppler ultrasonography (PDUS) to measure response to secukinumab treatment in patients with active psoriatic arthritis (PsA).
Sponsor and clinical phase	Novartis, Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Psoriatic arthritis is an autoimmune-mediated chronic inflammatory disease belonging to the spectrum of conditions commonly referred to as spondyloarthritides (SpA). Grayscale ultrasound coupled with power Doppler (PDUS) has been shown to be a sensitive imaging technology for assessing joint and entheseal involvement in PsA; however, there has been limited focus on its use for extensive evaluation of these structures in randomized controlled trials. The use of PDUS for monitoring pathological findings indicative of joint inflammation or enthesitis in patients with moderate-to-severe PsA has been demonstrated for patients treated with anti-tumor necrosis factor alpha (anti-TNFα) therapy in open label studies. This study is designed to leverage the sensitivity of ultrasonography available in clinical practice setting to better describe the time course of response to secukinumab (150 mg and 300 mg) on joint synovitis and enthesitis in PsA patients with an inadequate response (IR) to non-biologic DMARDs. PDUS changes in joint synovitis will be assessed using the global Outcome Measures in Rheumatology (OMERACT)-European League Against Rheumatism (EULAR) synovitis score (GLOESS) and changes in joint enthesitis will be assessed using the OMERACT enthesitis score.
Primary objective	• To demonstrate that there is a difference between secukinumab and placebo in terms of joint synovitis response over 12 weeks as measured by the PDUS global OMERACT-EULAR synovitis score (GLOESS) of the affected joints (out of 48 joints) in PsA patients with an IR to non-biologic DMARDs.
Secondary objectives	Key secondary objectives • To demonstrate that the efficacy of secukinumab at Week 12 is superior to placebo based on the proportion of patients achieving an American College of Rheumatology (ACR) 20 response. • To demonstrate that the efficacy of secukinumab at Week 12 is superior to placebo based on the proportion of patients achieving an ACR 50 response. • To demonstrate that the clinical response of secukinumab at Week 12 is superior to placebo based on the change in Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index from Baseline to Week 12. Other secondary objectives

	• To evaluate the therapeutic effect of secukinumab versus placebo on joint synovitis from Baseline to Week 8 using the GLOESS score out of 48 joints. • To evaluate the therapeutic effect of secukinumab versus placebo on enthesitis at Week 12 using the OMERACT enthesitis score for each affected enthesis. • To evaluate the overall safety, tolerability and immunogenicity of secukinumab.

Exploratory objectives	• To evaluate the therapeutic effect on joint synovitis for patients in the placebo group once switched to secukinumab from Week 12 to Week 24 and Week 24 to Week 52, as assessed by the improvement in synovitis from Week 12 to 24 and Week 24 to Week 52 using the GLOESS score and its components out of 48 joints.
	• To evaluate the therapeutic effect on joint synovitis in the initial secukinumab group as assessed by the improvement in synovitis from Baseline to Week 24 and to Week 52 using the GLOESS score and its components out of 48 joints.
	• To evaluate the therapeutic effect on enthesitis for patients in the placebo group who switched to secukinumab from Week 12 to Week 24 and Week 24 to Week 52 using the OMERACT individual enthesitis score and its morphologic components.
	• To evaluate the therapeutic effect on enthesitis for patients in the initial secukinumab group from Baseline to Week 24 and from Week 24 to Week 52 using the OMERACT individual enthesitis score and its morphologic components.
	• To explore the correlation between clinical improvement of each enthesitis site as assessed by SPARCC and the improvement in enthesitis as assessed by individual PDUS enthesitis scores from Baseline to Week 12.
	• To explore the correlation between the PDUS response versus ACR 20 response either by an improvement of the total GLOESS score of at least 20% from Baseline to 12 weeks or by comparing the clinical improvement in the same joints examined to GLOESS score.
	• To explore the correlation between the PDUS response versus the SPARCC score over 12 weeks by comparing the improvement in the same entheses examined.
	• To explore the efficacy of secukinumab at Week 24, during the extension period, and other time points for assessments that are not part of the primary and secondary objectives as applicable only to:
	  • ACR 20, ACR 50, ACR 70, ACR components, PASI 75, PASI 90, dactylitis count, HAQ-DI© response.
	  • Proportion of patients achieving minimal disease activity (MDA) at Week 24 and Week 52.
	[redacted]

	[redacted]
Study design	This is a 52-week, multicenter, international study consisting of a 1 to 4-week Screening period, a 12-week, placebo-controlled, double-blind treatment period, a 12-week open-label treatment period, and a 6-month open-label extension period.
Population	The study population will consist of male and female patients aged ≥ 18 years with PsA as per the classification criteria for PsA (CASPAR),and with active PsA for at least 6 months who must have a tender joint count (TJC) ≥ 3 out of 78 and swollen joint count (SJC) ≥ 3 out of 76 at Baseline and with an IR to non-biologic DMARDs. Patients can be re-screened only once and 'no' re-screening study related procedures should be performed prior to written re-consent by the patient. Mis-randomized patients cannot be re-screened.
Inclusion criteria	Patients eligible for inclusion in this study have to fulfill all of the following criteria: 1. Patient must be able to understand and communicate with the Investigator and comply with the requirements of the study and must provide written, signed and dated informed consent before any study assessment is performed. 2. Male or female patients at least 18 years of age. 3. Diagnosis of PsA as per CASPAR criteria with active PsA for at least 6 months and a TJC ≥ 3 of 78 and SJC ≥ 3 of 76 at Baseline. 4. a) Patients must have a total synovitis PDUS score ≥ 2 and inflammation related to PD signal **≥ 2 for at least 1 affected joint** (as observed via PDUS) of 48 joints at the Screening visit and at the Baseline visit (before injection), OR b) Patients must have a total synovitis PDUS score ≥ 2 and inflammation related to PD signal **≥ 1 for at least 2 affected joints** (as observed via PDUS) of 48 joints at the Screening visit and at the Baseline visit (before injection). 5. At least 1 clinically-involved enthesitis site at Screening and at the Baseline visit (before injection) defined by SPARCC index different from 0. 6. Rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) negative at Screening. 7. Patients with PsA who have had an IR to non-biologic DMARDs. 8. Patients with PsA who are taking NSAIDs should be on a stable dose for at least 2 weeks prior to enrollment and remain on a stable dose throughout the 24-week study period unless rescue therapy is needed. 9. Patients with PsA who are taking steroids must have received steroids at least 3 months prior to the Baseline visit and be on a

	stable dose of ≤ 10 mg equivalent prednisone for at least 4 weeks prior to Baseline visit and remain on a stable dose throughout the 24-week study period unless tolerance issues are present. 10. Patients with PsA who are taking MTX or DMARDs must have received them at least 3 months prior to Baseline visit and be on a stable dose of ≤ 25 mg/week of MTX or stable standard doses of other DMARD(s) (according to the Investigator's judgment) for at least 4 weeks prior to the Baseline visit and remain on a stable dose throughout the 24-week study period.
Exclusion criteria	Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the Investigator in order to ensure that the study population will be representative of all eligible patients. 1. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process obtained within 3 months prior to Screening and evaluated by a qualified physician. 2. Previous exposure to secukinumab or other biologic drug directly targeting interleukin 17 (IL-17) or IL-17 receptor. 3. Patients taking high-potency opioid analgesics (e.g. methadone, hydromorphone, morphine). 4. Use of any investigational drug and/or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug, whichever is longer. 5. Any change in the dose of oral corticosteroids in the last 4 weeks prior to the Baseline visit or use of i.v. intramuscular or intra-articular corticosteroid during the last 4 weeks prior to the enrollment visit. 6. Patients who have previously been treated with TNFα inhibitors (investigational or approved). 7. History of hypersensitivity to the study drug or its excipients or to drugs of similar classes. 8. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19). 9. Prohibited psoriasis treatments/medications with topical corticosteroids in the last 4 weeks prior to randomization (see Section 5.5.8 of main protocol). 10. 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. 11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g. 20 weeks in 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) or tubal ligation at least 6 weeks before taking study 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) with spermicidal foam/gel/film/cream/vaginal suppository. • Use of oral, 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. • Placement of an intrauterine device or intrauterine system. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study drug. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or surgical bilateral oophorectomy (with or without 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. 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 immunocompromise the patient and/or place the patient 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 (as per Investigator's judgment). 15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFT) such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), 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 laboratory 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. In any case, serum bilirubin should not exceed 1.6 mg/dL (27 µmol/L). 16. History of renal trauma, glomerulonephritis, or patients with 1 kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 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 2 weeks (exception: common cold) prior to randomization. 19. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5 mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated. 20. Known infection with human immunodeficiency virus, hepatitis B or hepatitis C at Screening or randomization. 21. 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). 22. Current severe progressive or uncontrolled disease, which in the judgment of the clinical Investigator renders the patient unsuitable for the trial. 23. Inability or unwillingness to undergo repeated venipuncture (e.g. because of poor tolerability or lack of access to veins). 24. Any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol. 25. Donation or loss of 400 mL or more of blood within 8 weeks before randomization. 26. History or evidence of ongoing alcohol or drug abuse, within the last 6 months before randomization. 27. Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization.
Investigational and reference therapy	Investigational treatment secukinumab 150 mg provided in 1 mL prefilled syringes (PFSs) or 300 mg provided in (2 × 1.0 mL PFSs of 150 mg dose). Dosing will be performed based on the severity of skin lesions. Reference treatment: secukinumab placebo provided in a 1 mL PFSs.
Efficacy assessments	• OMERACT/EULAR global synovitis score (GLOESS) and its components. • OMERACT enthesitis score and its components. • American College of Rheumatology (ACR) 20, 50 and 70 responses. • Swollen joint count (SJC)/tender joint count (TJC). • Patient's global assessment of disease activity (VAS). • Physician's global assessment (PGA) of disease activity (VAS). • Patient's assessment of PsA pain intensity (VAS). • Health assessment questionnaire – disability index (HAQ-DI©). • Minimal disease activity (MDA).

	• Spondyloarthritis Research Consortium of Canada (SPARCC). • Psoriasis area and severity index (PASI). • Leeds Dactylitis Index (LDI).
Safety assessments	• Incidence and severity of AEs/ SAEs. • Physical examinations. • Vital signs. • Height and weight. • QuantiFERON TB-Gold test or PPD skin test. • Local tolerability (injection site reactions). • Laboratory evaluations (hematology, clinical chemistry, urinalysis). • Pregnancy and assessment of fertility. • Tolerability of secukinumab. • Immunogenicity.
Other assessments	Not applicable.
Data analysis	The primary analysis variable is the change from baseline in Global PDUS score over 12 weeks. The primary analysis of this study will evaluate the superiority of secukinumab compared to placebo in PsA patients who have an IR to non-biologic DMARDs with respect to the change from Baseline in Global PDUS score over 12 weeks. The statistical hypothesis for the primary objective is that secukinumab is not different relative to placebo with respect to the change from baseline in GLOESS score over 12 weeks. Between-treatment differences in the change in GLOESS score will be evaluated using a mixed-effect model repeated measures (MMRM) with treatment regimen and analysis visit as factors and weight and baseline GLOESS score as continuous covariates. Treatment by analysis visit will be included as an interaction term in the model. An unstructured covariance structure will be assumed for this model. If the model does not converge, the compound symmetry covariance structure will be used.
Key words	Power Doppler ultrasonography, active psoriatic arthritis, secukinumab, enthesitis, synovitis, Phase 3b, monoclonal antibody, GLOESS score, ACR, CASPAR, OMERACT enthesitis score, SPARCC, PASI, PFS, HAQ-DI©, MDA, TJC, SJC, Physician's global assessment (PGA) of disease activity (VAS), Patient's assessment of PsA pain intensity (VAS), safety and tolerability.

1 Introduction

1.1 Background

1.1.1 Overview of psoriatic arthritis

Psoriatic arthritis (PsA) is an immune-mediated chronic inflammatory disease belonging to the spectrum of conditions commonly referred to as spondyloarthritides (SpA), which encompass a spectrum of overlapping clinical entities (Moll and Wright 1973). PsA is characterized by the association of peripheral arthritis, axial involvement and periarticular inflammation in patients with psoriasis. In addition to a heterogeneous and variable clinical course, PsA is complex and multifaceted and may include prominent involvement in the peripheral and axial diarthrodial joints, the skin and nails, and in periarticular structures such as the entheses. Simultaneous inflammation in the skin and musculoskeletal structures in a single patient, a relatively common scenario, often leads to a marked decrease in function and quality of life (Coates et al 2014).

Synovitis is a key manifestation of PsA and is associated with the development of joint erosion and structural damage. Peripheral enthesitis, an important feature that can be observed in all forms of SpA, usually manifests as isolated pain or tenderness at physical examination but is sometimes only detected by imaging techniques. One major hurdle faced by clinicians is their inability to establish an early diagnosis because of the poor specificity of symptoms (D'Agostino et al 2011). Peripheral enthesitis is frequently associated with the presence of psoriasis even in patients with early SpA (Richette et al 2013).

1.1.2 Treatment of psoriatic arthritis

Typically diseases modifying anti-rheumatic drugs (DMARDs) are used for the treatment of PsA including methotrexate (MTX), sulfasalazine, cyclosporine, and leflunomide; however, these are often inadequate because DMARDs only partially control established disease (Mease 2008). Tumor necrosis factor (TNF) blocking therapy was successfully introduced for the treatment of patients with PsA (Mease et al 2000). Interleukin-17 (IL-17) blocking therapies have more recently been introduced to provide better disease control and long term prevention of structural damage beyond mere abrogation of inflammatory processes.

Cosentyx® (secukinumab) is a recombinant monoclonal antibody, which neutralizes the activity of IL-17A, and has been shown to be effective in treating patients with moderate-to-severe plaque psoriasis. Secukinumab is approved in Europe (since Nov 2015), the US (since Jan 2016) and Canada (since Apr 2016) as well as in other countries including Mexico, Argentina, and Columbia for the treatment of PsA and ankylosing spondylitis (AS). Additionally, it is approved in Europe (since Jan 2015), the US (since Jan 2015) and Canada (since Mar 2015), as well as in other countries including Mexico, Argentina and Columbia, for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy (US and Canada only).

The approval of secukinumab for psoriasis was based on the safety and efficacy results from more than 10 Phase 2 and Phase 3 studies which included nearly 4 000 patients with moderate-to-severe plaque psoriasis (Langley et al 2014, Blauvelt et al 2014, Paul et al 2014). The four Phase 3, randomized, placebo-controlled studies, i.e. ERASURE, FIXTURE (Langley et al 2014), FEATURE (Blauvelt et al 2014) and JUNCTURE (Paul et al 2014), included 2403 patients with moderate-to-severe plaque psoriasis.

The approval of secukinumab for PsA was based on 2 pivotal Phase 3 secukinumab studies, i.e. FUTURE 1 (CAIN457F2306) and FUTURE 2 (CAIN457F2312) have been performed in 1003 patients with PsA (Mease et al 2014, McInnes et al 2015). These studies provided evidence that the secukinumab 150 mg regimen has a rapid onset of effect and demonstrates sustained improvement in all clinical domains of PsA up to Week 104 in FUTURE 2 (Mc Innes et al 2016: ACR Abstract No. 2757) and 3 years in FUTURE 1 (Mease et al 2016: ACR Abstract No. 961). These domains include signs and symptoms (both for arthritic and skin symptoms), structural damage (FUTURE 1 only), patient reported outcomes, physical function and QoL. The secukinumab 300 mg s.c. regimen enabled a subgroup of PsA patients with concomitant moderate-to-severe plaque psoriasis to achieve clear/almost clear skin, and demonstrated clinically meaningful benefit on the primary and multiple secondary endpoints in a subgroup of patients who were TNFα inhibitor inadequate responders.

The FUTURE 1 (i.e. CAIN457F2306) study also demonstrated the ability of secukinumab to provide significant and sustained inhibition of joint structural damage at Week 24. Inhibition of structural damage was maintained with secukinumab treatment up to Week 104 (Kavanaugh et al 2016). Patients receiving secukinumab 150 mg s.c. starting at Week 24 achieved comparable inhibition of structural damage progression at Week 52 as patients receiving secukinumab iv-150 mg s.c. regimen up to Week 24.

In all studies, secukinumab demonstrated a favorable safety profile, with similar incidence and severity of adverse events (AEs) between secukinumab treatment arms (150 mg and 300 mg).

Further details are provided in Section 3.6.

1.1.3 Power Doppler ultrasonography for monitoring treatment response in psoriatic arthritis

In recent years, the International Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) underlined the importance of integrating clinical and imaging findings from a rheumatology and dermatology perspective for psoriatic patients (Kaeley et al 2011, Gutierrez et al 2012) given the multifaceted nature of the disease. The use of Power Doppler and Grayscale ultrasound (PDUS) is a promising, non-invasive imaging method to assess peripheral involvement of SpA, including PsA. This technique permits visualization of most of the relevant joint pathologies associated with SpA, including synovitis, bone erosions, peripheral enthesitis, bursitis, tenosynovitis and dactylitis with results from numerous studies suggesting it provides additional information to conventional radiographic or clinical examinations (D'Agostino 2012). It may provide a more accessible point of care alternative to magnetic resonance imaging (MRI) and is non-invasive for patients in clinical practice. It also has the advantage of being able to scan multiple joints in a short period of time.

The Outcome Measures in Rheumatology and the European League Against Rheumatism (OMERACT-EULAR) Ultrasound Task Force is a working group since 2004 to standardize the use of ultrasonography in rheumatoid arthritis (RA) and in SpA, including PsA (Bruyn et al 2015) and has developed a composite scoring system (the OMERACT-EULAR global synovitis score (GLOESS) as measured using PDUS) to detect and score synovitis. This score combines Grayscale-assessed synovial hyperplasia with an intra-synovial Power Doppler signal for evaluating synovial activity. The score has demonstrated validity and intra-

and inter-observer reliability in cross-sectional datasets, applicability to all joints and consistency between machines. The responsiveness of the OMERACT-EULAR composite PDUS score was demonstrated in biologic-naïve patients with RA treated with abatacept plus DMARDs during 24 weeks (D'Agostino et al 2012, Wakefield et al 2007). Regardless of the differences between PDUS scoring systems, data from published studies indicate these systems could be useful in monitoring early response to biologic treatment in patients with PsA (Naredo et al 2008, Iagnocco et al 2008, Terslev et al 2003, Filippucci et al 2006, Fiocco et al 2005, Fiocco et al 1996).

PDUS has also proven to be a valid and reliable means of evaluating spondyloarthritis enthesitis (de Miguel et al 2009; D'Agostino et al 2002, 2003 and 2011). The hallmark feature of enthesitis is an abnormal vascularization of entheses, which was exclusively detected in SpA (D'Agostino et al 2003 and 2011). Quantification of entheseal involvement by ultrasound is best undertaken using semi-quantitative scoring systems that combine both inflammatory and structural damage signs. The OMERACT group has developed an enthesitis score which has demonstrated to be reliable and which includes clear definition of each elementary component (Tersley et al 2014) Evidence supporting the possibility of using ultrasound in combination with PD for monitoring pathological findings indicative of joint or soft tissue involvement in patients with PsA has been demonstrated for patients treated with anti-TNFα therapy (adalimumab or infliximab) (de Agustin et al 2012, Gutierrez et al 2012). Improvements in vascularization and structural changes were shown in the heel and the retrocalcaneal bursa with anti-TNFα therapy (D'Agostino et al 2003).

PDUS has never been used in the secukinumab development studies in PsA (or any other secukinumab studies) and presents the advantage to be a sensitive and non-invasive imaging technique to fill gaps in imaging data on a multifaceted disease with joints, enthesitis, dactylitis and skin manifestations. PDUS will allow an in depth evaluation of joints and enthesitis inflammation and their morphological components. A randomized clinical study in patients with PsA with an inadequate response (IR) to non-biologic DMARD will provide for the first time comparative PDUS data on the early efficacy and time course of response to secukinumab versus placebo using the OMERACT-EULAR global synovitis score (GLOESS score) and the OMERACT enthesitis score. In an attempt to limit variability of synovitis scoring across sites, the completion of a training session will be required by all PDUS assessors at each center in order to be qualified for PDUS evaluation in this study as well as a quality control assessment of the GLOESS score during the study and at the end of the study as described in Section 6.4.1. This study will also confirm clinical response to treatment using standard assessment tools, such as the American College of Rheumatology (ACR) response and SPARCC enthesitis index.

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[redacted]

1.2 Purpose

The purpose of this study is to provide early efficacy data using ultrasound on joint synovitis and enthesitis in addition to clinical efficacy already demonstrated in patients with active PsA despite non-biologic DMARDs. This study is designed to leverage the sensitivity of ultrasonography available in clinical practice setting to better describe the time course of response to secukinumab (150 mg and 300 mg) on joint synovitis and enthesitis in PsA patients with an IR to non-biologic DMARDs. [redacted]

2 Study objectives

2.1 Primary objective

- To demonstrate that there is a difference between secukinumab and placebo in terms of joint synovitis response over 12 weeks as measured by the PDUS Global OMERACT-EULAR Synovitis Score (GLOESS) of the affected joints (out of 48 joints) in PsA patients with an IR to non-biologic DMARDs.

2.2 Secondary objectives

2.2.1 Key secondary objectives

- To demonstrate that the efficacy of secukinumab at Week 12 is superior to placebo based on the proportion of patients achieving an ACR 20 response.
- To demonstrate that the efficacy of secukinumab at Week 12 is superior to placebo based on the proportion of patients achieving an ACR 50 response.
- To demonstrate that the clinical response of secukinumab at Week 12 is superior to placebo based on the change in SPARCC enthesitis index from Baseline to Week 12.

2.2.2 Other secondary objectives

- To evaluate the therapeutic effect of secukinumab versus placebo on joint synovitis from Baseline to Week 8 using the GLOESS score out of 48 joints.
- To evaluate the therapeutic effect of secukinumab versus placebo on enthesitis at Week 12 using the OMERACT enthesitis score for each affected enthesis.
- To evaluate the overall safety, tolerability and immunogenicity of secukinumab.

2.3 Exploratory objectives

- To evaluate the therapeutic effect on joint synovitis for patients in the placebo group once switched to secukinumab from Week 12 to Week 24 and Week 24 to Week 52, as assessed by the improvement in synovitis from Week 12 to 24 and Week 24 to Week 52 using the GLOESS score and its components out of 48 joints.
- To evaluate the therapeutic effect on joint synovitis in the initial secukinumab group as assessed by the improvement in synovitis from Baseline to Week 24 and to Week 52 using the GLOESS score and its components out of 48 joints.
- To evaluate the therapeutic effect on enthesitis for patients in the placebo group who switched to secukinumab from Week 12 to Week 24 and Week 24 to Week 52 using the OMERACT individual enthesitis score and its morphologic components.
- To evaluate the therapeutic effect on enthesitis for patients in the initial secukinumab group from Baseline to Week 24 and from Week 24 to Week 52 using the OMERACT individual enthesitis score and its morphologic components.
- To explore the correlation between clinical improvement of each enthesitis site as assessed by SPARCC and the improvement in enthesitis as assessed by individual PDUS enthesitis scores from Baseline to Week 12.
- To explore the correlation between the PDUS response versus ACR 20 response either by an improvement of the total GLOESS of at least 20% as compared to Baseline over 12 weeks or by comparing the improvement in the same joints examined.
- To explore the correlation between the PDUS response versus the SPARCC score over 12 weeks by comparing the improvement in the same entheses examined.
- To explore the efficacy of secukinumab at Week 24, during the extension period, and other time points for assessments that are not part of the primary and secondary objectives as applicable only to:
  - ACR 20, ACR 50, ACR 70, ACR components, PASI 75, PASI 90, dactylitis count, HAQ-DI© response.
  - Proportion of patients achieving minimal disease activity (MDA) at Week 24 and Week 52.

2.3.1 Sub-study objectives

The following exploratory objectives will be evaluated in the substudy:

[redacted]

[redacted]

3 Investigational plan

3.1 Study design

This is a 52-week, multicenter, international study consisting of a 1 to 4-week Screening period, a 12-week randomized, placebo-controlled double-blind treatment period (Period 1 [Baseline to Week 12]), a 12-week open-label treatment period (Period 2 [Week 12 to Week 24]), a 6-month open-label extension period (Period 3 [Week 24 to Week 52]), and a 12-week follow-up period (Week 52 to Week 64).

During the entire study, it is mandatory for the integrity of study data to maintain the blind even between the Ultrasonography Investigator and the Clinical Investigator. This ensures that the PDUS assessment is performed without the knowledge of current clinical symptoms of the patient. The PDUS assessment will be performed by a rheumatologist who is unaware of the clinical symptoms, and randomization arm of the study patient.

Screening period

Informed consent: Investigators must ensure that patients, or, in those situations where consent cannot be given by patients, their legally acceptable representative, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding this clinical study. Freely given written informed consent must be obtained from every patient or, in those situations where consent cannot be given by patients, their legally acceptable representative, prior to clinical study participation, including informed consent for any Screening procedures conducted to establish patient eligibility for the study. The rights, safety, and well-being of the study patients are the most important considerations and should prevail over interests of science and society. See Section 10.2 for further details.

Eligible patients will be enrolled and enter a 1- to 4-week Screening period prior to randomization. In the case of leflunomide, the washout period is 8 weeks unless patients take cholestyramine according to the manufacturer's recommendation where the washout period is less than 4 weeks. Patients who received MTX or other DMARDs during the last 3 months prior to Screening will continue with their previous therapy until Week 24.

Treatment periods

During the study, the study treatment (secukinumab 150 mg and 300 mg, and placebo) provided as prefilled syringes (PFSs) will be self-administered s.c. (into the appropriate injection site of the body) by the patient at the study center during Treatment Period 1 and Treatment Period 2 under supervision of the Investigator/ qualified study center staff; and at home at Week 28, 32, 40, 44, and 48 (during the Extension Period) as indicated in Table 6-1 and Table 6-2 and described in Section 5.5.4.

At each study visit, all patients will receive 2 s.c. injections using PFSs since secukinumab is available in 1.0 mL PFSs. Patients assigned to secukinumab 150 mg will receive 1 PFS of secukinumab 150 mg and 1 PFS of placebo; patients assigned to secukinumab 300 mg will

receive 2 PFS of secukinumab 150 mg; and patients assigned to placebo will receive 2 PFSs of placebo. At the study visits preceding home administration, sufficient study drug will be supplied to the patient to cover home administrations.

Treatment period 1 – placebo-controlled double-blind (Baseline to Week 12)

At Baseline, patients whose eligibility is confirmed will be randomized in 1:1 ratio in a double-blinded fashion to one of 2 treatment groups as follows:

- **Group 1**: secukinumab (150 mg s.c. or 300 mg s.c. depending on severity of skin lesions) (1, 2)
  - secukinumab 150 mg (1.0 mL PFS of 150 mg dose) and placebo (1.0 mL PFS) administered at Baseline, Weeks 1, 2 and 3, followed by 4-weekly dosing at Week 4 and Week 8.
  - secukinumab 300 mg (2 × 1.0 mL PFSs of 150 mg dose) administered at Baseline, Weeks 1, 2 and 3, followed by 4-weekly dosing at Week 4 and Week 8.

1. Secukinumab 150 mg will be administered to patients with PsA (body surface area (BSA) ≤ 10% as assessed by PASI (Section 6.4.5), corresponding to mild psoriatic skin lesions).
2. Secukinumab 300 mg s.c. will be administered to patients with PsA (BSA > 10% as assessed by PASI (Section 6.4.5), corresponding to moderate-to-severe psoriatic skin lesions.

- **Group 2**: placebo
  - Placebo (2 × 1.0 mL PFSs) at Baseline, Weeks 1, 2 and 3, followed by 4-weekly dosing at Week 4 and Week 8.

Treatment Period 2 – open-label treatment period (Week 12 to Week 24)

At Week 12, the assessments to address the primary objective will be performed as outlined in Table 6-1. After each patient has completed the Week 12 assessments, the investigator staff will notify the Novartis clinical team and the Interactive Response Technology (IRT) system that open-label assessments are starting. Patient, relevant study center personnel and data analysts will be unblinded to the treatment patient will be getting from this period onwards (i.e. open label treatment from this period). From Week 12, secukinumab will be given open-label in order to eliminate the placebo injection (i.e. only 150 mg or 300 mg secukinumab will be dispensed as 1 or 2 PFSs, respectively).

In **Group 1**, patients will continue to receive the same active dose of secukinumab every 4 weeks until Week 24 (i.e. at Week 12, 16 and 20); patients will no longer receive the placebo PFS, which was administered to maintain blinding.

In **Group 2**, patients will commence open-label secukinumab every 4 weeks from Week 12, as follows, based on their clinical characteristics at Week 12:

- secukinumab (150 mg s.c. or 300 mg s.c. depending on severity of skin lesions)(1, 2)
  - secukinumab 150 mg (1.0 mL PFS of 150 mg dose) every 4 weeks starting from Week 12 (i.e. Week 12, 16 and 20).
  - secukinumab 300 mg (2 × 1.0 mL PFSs of 150 mg dose) every 4 weeks starting from Week 12 (i.e. Week 12, 16 and 20).

1. Secukinumab 150 mg will be administered to patients with PsA (BSA ≤ 10% as assessed by PASI (Section 6.4.5), corresponding to mild psoriatic skin lesions).

2. Secukinumab 300 mg s.c. will be administered to patients with PsA with BSA > 10% as assessed by PASI (Section 6.4.5), corresponding to moderate-to-severe psoriatic skin lesions).

A blinded sample size estimation (SSR) will be performed when the first 60 patients have completed the Week 12 visit as described in Section 9.6.

The Week 12 analysis will be performed after all patients complete the Week 12 visit (see Section 9.6). Only the data analysts will be unblinded to the Treatment Period 1 randomization after the Week 12 database lock/analyses. Summary results will be shared internally and externally; however, individual unblinded patient data will not be disclosed. The Ultrasonography Investigator and the Clinical Investigator will remain blinded from each other until the final database lock.

Treatment Period 3 – extension period (Week 24 to Week 52)

Treatment Period 3 is an extension period to allow responder patients (if they wish and as per clinician's judgment) the possibility to continue open-label secukinumab treatment up to Week 52. Patients must sign a separate ICF to confirm their agreement to participate in the extension period (Section 9.6).

At Week 24, open-label secukinumab will continue to be assigned to patients in Group 1 and Group 2 at the same dose every 4 weeks until Week 52 for administration at either the study site (i.e. Week 24, 36 and 52) or at home (Week 28, 32, 40, 44, and 48).

At **Week 24**, patients who do not reach at least a 20% improvement in tender joint count (TJC) and swollen joint count (SJC) with secukinumab (150 mg or 300 mg) from Baseline will be withdrawn from the study.

The Week 24 analysis will be performed after all patients complete the Week 24 visit (see Section 9.6).

The final analysis will be performed after the last patient has completed the Week 64/End of Study visit or early withdrawal visit (in case of early withdrawal of last patient from the study). After the final database lock and analyses have been completed, site personnel (including the Ultrasonography Investigator and Clinical Investigator) will be unblinded to the original randomized treatment (sequence) assignment at randomization. Additional study treatments (non-biologic DMARDs including MTX, systemic corticosteroids, and NSAIDs, low strength opioids, or paracetamol/acetaminophen) permitted for use alongside secukinumab in this study are described in Section 5.1.2.

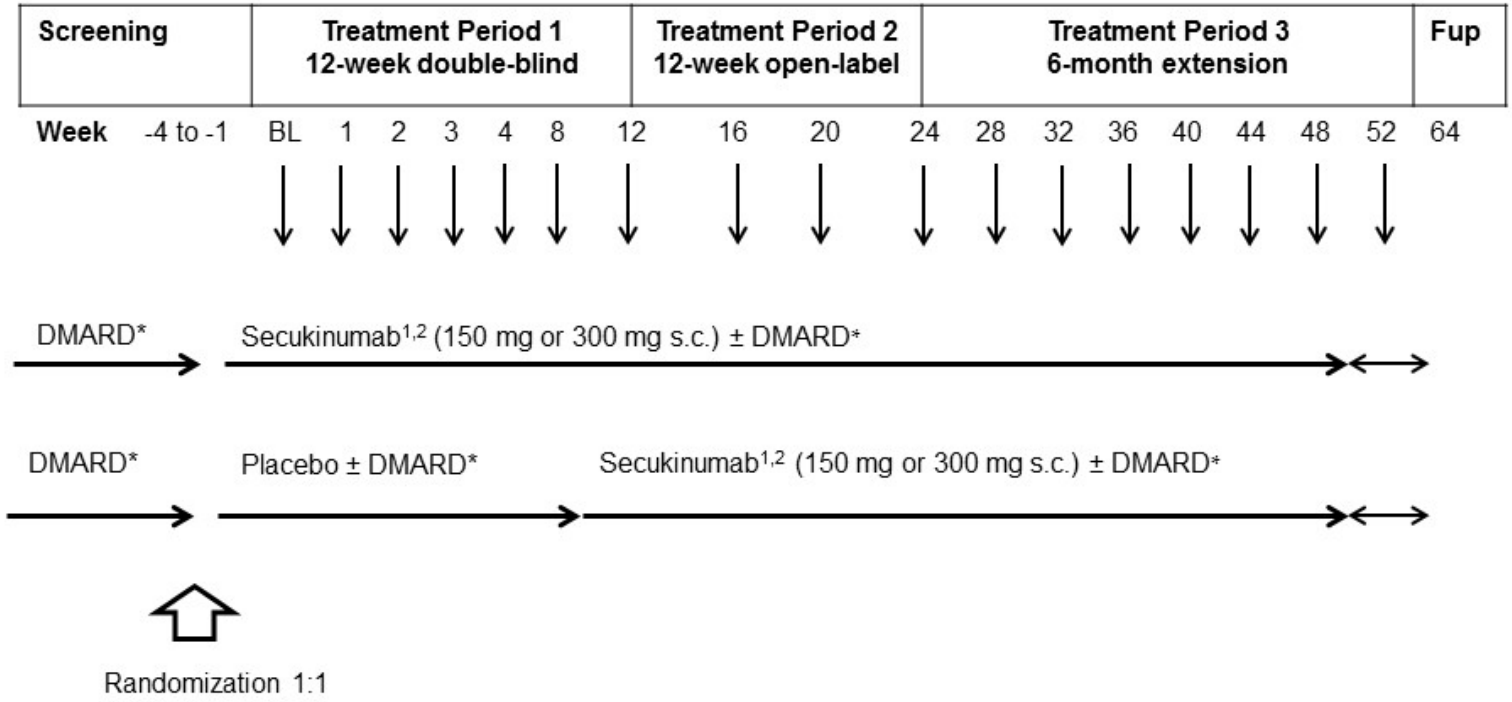
If, despite concomitant medication, a patient presents with worsening of disease or does not seem to benefit from study treatment, necessary rescue medication with low strength opioids or paracetamol/acetaminophen is permitted for use alongside secukinumab prior to completion of Week 24 assessments. In addition, changes in NSAID concomitant therapy are permitted prior to Week 24 assessments as per the Investigator's clinical judgment and following failure of previously authorized rescue medication.

If there is no patient improvement despite authorized rescue medication and there is a need to use prohibited treatments (as described in Table 5-2) prior to completion of Week 24 assessments, patients will be discontinued from the study and assessed as a prematurely withdrawn patient as described in Section 6 (i.e. the patient will return for the final visit

within the treatment period (4 weeks after the last study treatment), as well as return for the final follow-up visit (F64) 12 weeks after the last study treatment). Efficacy will be assessed in detail at every study visit; patients who are deemed not to be benefiting from the study treatment based upon safety and efficacy assessments by the Investigator, or for any reason of their own accord, will be free to discontinue participation in the study at any time.

A follow-up visit is to be done 12 weeks after last study treatment administration for all patients, regardless of whether they complete the entire study as planned or discontinue prematurely. All AEs that occur during this post-treatment follow-up period will be included in the evaluation of treatment-emergent AEs.

Figure 3-1 Study design



Abbreviations: DMARD: disease modifying anti-rheumatic drugs, Fup: follow-up

1 Secukinumab 150 mg will be administered to patients with PsA (BSA ≤ 10% as assessed by PASI (Section 6.4.5), corresponding to mild skin lesions).

2 Secukinumab 300 mg s.c. will be administered to patients with PsA (BSA > 10% as assessed by PASI (Section 6.4.5), corresponding to moderate-to-severe psoriatic skin lesions).

Note: Study drug will be self-administered by the patient (or caregiver if applicable) at home at Week 28, 32, 40, 44 and 48 (Section 5.5.4).

* Patients who received MTX/ other DMARDs at a stable dose in the last 3 months prior to Screening should remain on a stable dose until Week 24 unless there are safety or tolerability issues as described in Section 5.1.2.

Note: The Ultrasonography Investigator will be blinded from the Clinical Investigator in this study.

3.2 Rationale of study design

This study will consist of 3 study periods: a 12-week placebo-controlled double-blind period, a 12-week open label period and a 6-month open-label extension period.

Treatment Period 1 is a 12-week placebo-controlled, randomized period primarily designed to demonstrate the early and optimal efficacy of secukinumab vs placebo on joint synovitis using PDUS, which is a very sensitive imaging technique. It will also compare the improvement in joint inflammation response (synovitis and enthesitis) for secukinumab compared to placebo using PDUS, specifically via the GLOESS and global entheseal score, after 12 weeks of treatment in patients with active PsA with an IR to DMARDs.

The placebo control arm in the first period of this study is aimed at evaluating the variability of joint synovitis using the global OMERACT PDUS synovitis score and will allow the true effect of secukinumab treatment to be demonstrated. In addition, the 12-week placebo-controlled period is aligned with Phase 3 trials of other biologics and is in accordance with EMA guidelines (CHMP/EWP/438/04).

A TNFα inhibitor-naïve population was selected for this study despite efficacy being observed with secukinumab in patients previously treated with TNFα inhibitors as this is the first exploratory PDUS study in secukinumab; and a homogeneous population with biologically-naïve patients will limit data variability and will allow for better assessment of ultrasound and clinical outcomes.

The main aim of Period 2 is to assess the maintenance or increased magnitude of treatment response on joint synovitis for patients from the original secukinumab groups and to assess the time course of response with secukinumab on joint synovitis in the original placebo group switched to secukinumab from Week 12.

The main aim of Period 3 (Extension Period [Week 24 to Week 52]) is to allow patients who respond to secukinumab (if they wish and as per clinician's judgment) the possibility to extend study treatment up to Week 52. Clinical efficacy assessments (including PDUS assessments) and safety assessments are also extended to occur at Week 36 and Week 52 during this period. Other aims are to assess patients who may develop a late ultrasound response and/or clinical response to secukinumab and to further evaluate the long term maintenance of the clinical and ultrasound response to secukinumab.

Patients who are experiencing worsening of disease in any of the treatment groups can exit the study at their own request or based on the advice of the Investigator at any time.

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

The doses (150 mg and 300 mg), regimen (once weekly for first 4 weeks, followed by 4-weekly dosing from Week 4), route of administration (s.c.) and duration of treatment were chosen for this study in accordance with the outcomes of the Phase 3 trials in PsA (CAIN457F2306 and CAIN457F2312). In addition, 300 mg is approved in Europe for the treatment of PsA with concomitant moderate to severe psoriasis (per the EU SmPC) and moderate to severe psoriasis may be defined as > 10% BSA as per EMA guideline (CHMP/EWP/2454/02 corr).

In the Phase 3 trials in PsA, CAIN457F2306 assessed the efficacy of both 75 mg and 150 mg s.c. maintenance doses (every 4 weeks) after loading regimens consisting of 3 i.v. doses of

10 mg/kg given at Baseline, Week 2 and 4, and CAIN457F2312 assessed the efficacy of 75 mg, 150 mg and 300 mg s.c. maintenance doses (every 4 weeks) after loading regimens consisting of s.c. doses of 75 mg, 150 mg or 300 mg given at Baseline, Week 1, 2, and 3. Given the similarity of the ACR 20 response seen at the Week 24 primary endpoint for the 150 mg dose in each of these studies, regardless of whether the loading dosing was i.v. (CAIN457F2306: 50.0% for 150 mg vs 17.3% for placebo) or s.c. (CAIN457F2312: 51.0% for 150 mg vs 15.3% for placebo), 150 mg is considered a sufficient dose to provide clinically and statistically significant efficacy, whereas higher loading doses of secukinumab do not appear to confer a greater response on the primary endpoint of ACR 20 at Week 24. This study also demonstrated the ability of secukinumab to provide significant and sustained inhibition of joint structural damage at Week 24 and Week 52. Patients receiving secukinumab 150 mg s.c. starting at Week 24 achieved comparable inhibition of structural damage progression at Week 52 as patients receiving secukinumab iv-150 mg s.c. regimen up to Week 24.

In the CAIN457F2312 study, the PASI 75 and PASI 90 response was assessed in the subgroup of patients who had $\geq 3\%$ skin involvement with psoriasis at Baseline. For both PASI 75 and PASI 90 response rates, the difference to placebo at Week 24 was statistically significant for the secukinumab 150 mg and 300 mg doses (PASI 75: 48.3%, $p = 0.0006$ and 63.4%, $p < 0.0001$; PASI 90: 32.8%, $p = 0.0029$ and 48.8%, $p = 0.0002$, respectively). The percentage of responders increased as the secukinumab dose increased, with the secukinumab 300 mg dose demonstrating a clinically meaningful improvement over the secukinumab 150 mg dose (treatment differences between secukinumab 300 mg and 150 mg for PASI 75 and PASI 90 were 15.1% and 16%, respectively). Of note, the 75 mg s.c. loading/s.c. maintenance regimen tested in CAIN457F2312 achieved a statistically significant but clinically lower effect size in ACR 20 response of 29.3% and did not achieve statistically significant improvements in any of the other pre-specified secondary efficacy endpoints which included: PASI 75, PASI 90, DAS28-CRP, SF36 Physical Component Summary, HAQ-DI©, ACR 50, resolution of dactylitis and resolution of enthesitis.

Overall, the Phase 3 studies in PsA (CAIN457F2306 and CAIN457F2312) provide evidence that secukinumab 150 mg regimen is efficacious and demonstrates clinically meaningful improvement in all clinical domains of PsA. These domains include signs and symptoms (both for arthritic and skin symptoms), structural damage, patient reported outcomes, physical function, and quality of life. Secukinumab 300 mg s.c. regimen enabled a subgroup of PsA patients with concomitant moderate-to-severe plaque psoriasis to achieve clear/almost clear skin, and demonstrated clinically meaningful benefit on the primary and multiple secondary endpoints in a subgroup of patients who were TNFα inhibitor inadequate responders.

Pre-filled syringes have been selected for secukinumab s.c. administration in this study as these have been successfully used in the Phase 3 clinical studies in moderate-to-severe plaque psoriasis, as well as in the completed Phase 3 clinical studies for PsA (CAIN457F2306 and CAIN457F2312), which showed the use of PFSs was safe and well tolerated.

3.4 Rationale for choice of comparator

A placebo group is included in this study up to the Week 12. Due to the nature of the disease and the primary outcome measure to evaluate the time course of response to secukinumab for joint inflammation synovitis (OMERACT-EULAR global PDUS score out of 48 joints), a placebo group is necessary to obtain robust and reliable efficacy measurements for comparison between the active treatment groups and placebo in a controlled fashion up to 12 weeks and differentiate the true therapeutic effect from the variability of the disease. Patients assigned to placebo for the first 12 weeks in the study will be assigned to secukinumab for the next 12 weeks and will therefore have the opportunity to benefit from the proven efficacy of the active study drug.

Patients are permitted to continue their non-biologic DMARDs (including MTX) and systemic corticosteroid medications at a stable dose during the study up to Week 24 as described in Section 5.1.2.1, Section 5.1.2.2 and Section 5.1.2.3.

If, despite concomitant medication, a patient presents with worsening of disease or does not seem to benefit from study treatment, necessary rescue medication with low strength opioids or paracetamol/acetaminophen is permitted for use alongside secukinumab prior to completion of Week 24 assessments. Changes in NSAID concomitant therapy are permitted prior to Week 24 assessments as a rescue therapy as per the Investigator's clinical judgment and following failure of previously authorized rescue medication. Changes in NSAID concomitant therapy after Week 24 assessments are also permitted as per the Investigator's clinical judgment as described in Section 5.1.2.4.

3.5 Purpose and timing of interim analyses/design adaptations

A blinded sample size re-estimation (SSR) will be performed after the first 60 patients complete the Week 12 visit. The objective of the blinded SSR is to evaluate the assumptions of the sample size calculation and to decide whether the study should continue as planned. Details on the SSR options that will be considered can be found in Section 9.6.

The analysis of the primary and secondary efficacy variables will be performed after all patients complete the Week 12 visit. This analysis will also include exploratory variables outlined up to Week 12 and all available safety data. Subsequent to the Week 12 analysis, a Week 24 analysis will be performed and a final analysis will be performed after the final database lock, i.e. when last patient completes the Week 64/End of Study visit or early withdrawal visit.

3.6 Risks and benefits

Secukinumab is approved in Europe (since Nov 2015), the US (since Jan 2016), Canada (since Apr 2016), as well as in other countries, including Mexico, Argentina, and Columbia for the treatment of PsA and AS. Additionally, it is approved in Europe (since Jan 2015), the US (since Jan 2015) and Canada (since Mar 2015), as well as in other countries including Mexico, Argentina and Columbia, for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy (US and Canada only).

Secukinumab has shown either preliminary or confirmed efficacy in several inflammatory diseases including PsA, psoriasis and AS. The primary and key secondary efficacy endpoints for secukinumab were met in both Phase 3 randomized clinical trials in PsA (CAIN457F2306 and CAIN457F2312). Both trials were adequately powered to detect clinically meaningful

improvement in efficacy compared to placebo. Both trials used pre-specified hierarchical testing schemes to control for multiplicity of comparisons. The efficacy of secukinumab 150 mg and 300 mg s.c. load followed by respective maintenance was robust and similar across multiple endpoints, with clinically meaningful improvements in signs and clinical symptoms, physical function, disease activity, skin involvement, patient-reported outcomes and measures of productivity. The therapeutic effect was rapid (within 3 weeks) and sustained. Moreover, these benefits were observed in the overall PsA population comprising subpopulations of both PsA patients naïve to anti-TNFα therapy and anti-TNFα IR (30% to 40%). The 300 mg s.c. dose provided greater clinical benefit in anti-TNFα IR patients and patients with concomitant moderate-to-severe plaque psoriasis. The 75 mg s.c. dose was ineffective.

The safety profile observed in the latest drug safety update report (DSUR) (Issue 008: 26-Jun-2017 to 25-Jun-2018) is in line with the current known safety profile of secukinumab in PsA, moderate to severe psoriasis, and AS. As of 25-Jun-2018, approximately 24279 subjects (which included patients and a small number of healthy volunteers) had been enrolled with the secukinumab clinical development program (including trials where secukinumab had been used as a protocol specified treatment), of which approximately 20000 subjects (comprised of patients and healthy volunteers) had received at least 1 dose of secukinumab. Overall, healthy subjects and patients suffering from PsA, psoriasis, rheumatoid arthritis, AS, nr-axial SpA, multiple sclerosis, uveitis, dry eye, Crohn's disease, asthma and polymyalgia rheumatica have received secukinumab at doses ranging from single and multiple iv doses of 0.1 mg/kg up to 30 mg/kg and s.c. doses of 25 mg up to 300 mg. The cumulative patient exposure since the first launch of secukinumab is estimated to be approximately 212060 patient years.

Full safety results from all PsA, AS and psoriasis completed studies show that secukinumab generally is safe and well tolerated. For these indications, secukinumab has shown a higher rate of total AEs, mainly infections, when compared to placebo (placebo-controlled periods of 12 to 16 weeks depending on the protocol). The majority of infections were upper respiratory tract infections. However, no clinically meaningful difference was observed in infectious SAEs. In addition, no dose dependency with secukinumab (300 mg and 150 mg) was observed in the overall rate of infections or upper respiratory tract infections.

Adverse drug reactions (ADRs) classified as very common (≥ 1/10 patients) or common (≥ 1/100 but < 1/10 patients) included upper respiratory tract infections (nasopharyngitis, upper respiratory tract infection, rhinitis and pharyngitis), oral herpes, rhinorrhea, diarrhea and urticaria. Uncommon (≥ 1/1000 but < 1/100 patients) ADRs included sinusitis, tonsillitis, oral candidiasis, tinea pedis, neutropenia and conjunctivitis.

Infections, neutropenia and hypersensitivity are important identified risks, while malignancies, major adverse cardiovascular events, immunogenicity, Crohn's disease, and hepatitis B reactivation (EU only) are important potential risks. Interaction with live vaccines is an important potential risk.

Immunogenicity was low with secukinumab and did not correlate with loss of efficacy in all indications studied to date. No new and relevant information from clinical trials was obtained for any of the above topics during the reporting interval for the latest DSUR and the overall post-marketing experience (including reporting rates across Periodic Safety Update Reports

(PSURs) 1, 2, 3 and cumulative period) has been in line with what was observed during the clinical program.

During the reporting interval of the latest DSUR, a Risk Management Plan (RMP) update was triggered upon request from Pharmacovigilance Risk Assessment Committee, to include suicidal ideation and behavior (SIB) as an important potential risk in the RMP on the basis that "although causality has not been established, SIB meets the criteria as important potential risk because a potential biological mechanism cannot be completely ruled out since the biological role of IL-17 receptor ligands is still largely unknown, and consideration of the potential public health impact". The RMP is currently being updated for this change. At its completion SIB will be listed as an important potential risk in the RMP.

From the standpoint of the overall risk-benefit assessment, the current trial is justified. The risk to patients in this study will be minimized by compliance with the eligibility criteria and study procedures and close clinical monitoring.

4 Population

The study population will consist of male and female patients aged ≥ 18 years with PsA as per the classification criteria for PsA (CASPAR) and with active PsA for at least 6 months and must have ≥ 3 tender joint count (TJC) out of 78 and ≥ 3 swollen joint count (SJC) out of 76 at Baseline and with an IR to non-biologic DMARDs. Patients can be re-screened only once and 'no' re-screening study related procedures should be performed prior to written re-consent by the patient. Mis-randomized patients cannot be re-screened.

The goal is to randomize 164 patients in total (82 patients per arm) at approximately 50 centers worldwide.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Patient must be able to understand and communicate with the Investigator and comply with the requirements of the study and must provide written, signed and dated informed consent before any study assessment is performed.
2. Male or female patients at least 18 years of age.
3. Diagnosis of PsA as per CASPAR with active PsA for at least 6 months and a TJC ≥ 3 of 78 and SJC ≥ 3 of 76 at Baseline.
4. a) Patients must have a total synovitis PDUS score ≥ 2 and inflammation related to PD signal **≥ 2 for at least 1 affected joint** (as observed via PDUS) of 48 joints at the Screening visit and at the Baseline visit (before injection), OR

   b) Patients must have a total synovitis PDUS score ≥ 2 and inflammation related to PD signal **≥ 1 for at least 2 affected joints** (as observed via PDUS) of 48 joints at the Screening visit and at the Baseline visit (before injection).
5. At least 1 clinically-involved enthesitis site at Screening and at the Baseline visit (before injection) defined by SPARCC index different from 0.
6. Rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) negative at Screening.
7. Patients with PsA who have an IR to non-biologic DMARDs.

8. Patients with PsA who are taking NSAIDs should be on a stable dose for at least 2 weeks prior to enrollment and remain on a stable dose throughout the 24-week study period unless rescue therapy is needed.
9. Patients with PsA who are taking steroids must have received steroids at least 3 months prior to the Baseline visit and be on a stable dose of ≤ 10 mg equivalent prednisone for at least 4 weeks prior to Baseline visit and remain on a stable dose throughout the 24-week study period unless tolerance issues are present.
10. Patients with PsA who are taking MTX or DMARDs must have received them at least 3 months prior to Baseline visit and be on a stable dose of ≤ 25 mg/week of MTX or stable standard doses of other DMARD(s) (according to the Investigator's judgment) for at least 4 weeks prior to the Baseline visit and remain on a stable dose throughout the 24-week study period.

4.2 Exclusion criteria

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

1. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process obtained within 3 months prior to Screening and evaluated by a qualified physician.
2. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor.
3. Patients taking high-potency opioid analgesics (e.g. methadone, hydromorphone, morphine).
4. Use of any investigational drug and/or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug, whichever is longer.
5. Any change in the dose of oral corticosteroids in the last 4 weeks prior to the Baseline visit or use of i.v. intramuscular or intra-articular corticosteroid during the last 4 weeks prior to the enrollment visit.
6. Patients who have previously been treated with TNFα inhibitors (investigational or approved).
7. History of hypersensitivity to the study drug or its excipients or to drugs of similar classes.
8. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19).
9. Prohibited psoriasis treatments/medications with topical corticosteroids in the last 4 weeks prior to randomization (see Section 5.5.8).
10. 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.
11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g. 20 weeks in 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) or tubal ligation at least 6 weeks before taking study 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) with spermicidal foam/gel/film/cream/vaginal suppository.
- Use of oral, 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.
- Placement of an intrauterine device or intrauterine system.

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

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or surgical bilateral oophorectomy (with or without 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.

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 immunocompromise the patient and/or place the patient 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), uncontrolled diabetes (as per Investigator's judgment).
15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFT) such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), 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 laboratory 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. In any case, serum bilirubin should not exceed 1.6 mg/dL (27 μmol/L).

16. History of renal trauma, glomerulonephritis, or patients with 1 kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 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 2 weeks (exception: common cold) prior to randomization.
19. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5 mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test (as indicated in Section 6.5.4 and Table 6-1).
20. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.
21. Known infection with human immunodeficiency virus, 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 patient 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 6 months before randomization.
28. Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization.

5 Treatment

Secukinumab for s.c. injection will be supplied in single boxes each containing PFSs of 150 mg secukinumab in a 1 mL liquid formulation. The solution for injection in the PFS is colorless to slightly yellow.

Each 300 mg dose will be administered as 2 PFS injections of 150 mg secukinumab. All study drugs will be labelled appropriately.

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Novartis will supply the following:

- Investigational treatment

Secukinumab 150 mg provided in 1 mL PFS for s.c. injection. The 300 mg dose will be administered as 2 × PFS injections.

- Reference treatment

Secukinumab placebo provided in a 1 mL PFS for s.c. injection.

Patients will be instructed by site staff on how to self-administer the s.c. injection using the PFS based on the Instructions for Use (IFU). The study treatment (secukinumab (150 mg and 300 mg) and placebo provided as PFSs) will be self-administered s.c. (into the appropriate injection site of the body) by the patient at the study center during Treatment Period 1 and Treatment Period 2 under supervision of the Investigator/ qualified study center staff, or at home at Week 28, 32, 40, 44, and 48 (during Treatment Period 3: Extension Period) as indicated in Table 6-1 and Table 6-2.

At each study treatment visit, all patients will receive 2 s.c. injections using PFSs since secukinumab is available in 1 mL PFSs. Patients assigned to secukinumab 150 mg will receive 1 PFS of secukinumab 150 mg and 1 PFS of placebo; patients assigned to secukinumab 300 mg will receive 2 PFS of secukinumab 150 mg; and patients assigned to placebo will receive 2 PFSs of placebo. At the study visits preceding home administration, sufficient study drug will be supplied to the patient to cover home administrations.

The PFSs are packed in a double-blinded fashion and do not need to be prepared. The study treatments will be labeled as follows:

- Double-blind secukinumab and placebo PFSs will be labeled AIN457 150 mg /1 mL/Placebo for dosing until Week 12.
- Open label secukinumab PFSs will be labeled AIN457 150 mg/1 mL.

For detailed instructions for storage of the study treatments, please refer to Section 5.5.3.

5.1.2 Additional study treatment

During this study, MTX or other DMARDs, systemic corticosteroids, and NSAIDs, low strength opioids, or paracetamol/acetaminophen are permitted as described in the sub-sections below.

5.1.2.1 Disease-modifying anti-rheumatic drugs

Background non-biologic DMARDs must have been initiated at least 3 months prior to the Baseline visit and should be taken at standard stable doses (according to the Investigator's judgment) for at least 4 weeks prior to the Baseline visit. Non-biologic DMARDs can be continued at a stable dose until Week 24 unless there are safety or tolerability issues.

5.1.2.2 Methotrexate

Methotrexate at a stable dose of up to 25 mg/week until Week 24 with folic acid supplementation is permitted only for patients who started to receive MTX at least 3 months prior to enrollment and were on a stable dose for at least 4 weeks prior to enrollment. The dose may be decreased only due to toxicity. The weekly dose of MTX should be taken more than 48 hours before any clinical laboratory evaluation.

After Week 24, the dose and regimen of MTX may be modified as per Investigator's judgment and patient need.

Patients on MTX must be taking folic acid supplementation before randomization and during the study to minimize the likelihood of MTX-associated toxicity.

5.1.2.3 Systemic corticosteroids

Treatment with systemic corticosteroids is permitted up to a maximum daily dosage of 10 mg prednisone equivalent only if the corticosteroid was started 3 months prior to enrollment and the dose was stable for at least 4 weeks prior to enrollment. The patient should remain on a stable dose until Week 24. After Week 24, the dose and regimen of systemic corticosteroids may be modified as per the Investigator's judgment and patient needs.

Corticosteroid dose reductions below 10 mg prednisone equivalent are permitted after Week 24, although the corticosteroid dose should not be reduced by more than 1 mg prednisone equivalent every 4 weeks. Any change in the dose of systemic corticosteroids during the study must be recorded on the corresponding electronic CRF (eCRF) page.

Table 5-1 Corticosteroids conversion table for the equivalence of 1 mg of cortisone

Corticosteroid	Equivalence of 1 mg of cortisone
Cortisone	1 mg
Prednisone, prednisolone	0.2 mg
Methylprednisone, triamcinolone	0.16 mg
Dexamethasone	0.03 mg
Fludrocortisone	0.08 mg
Deflazacort	0.24 mg
Paramethasone	0.08 mg
Hydrocortisone, cortisol	0.8 mg

Sources:
Asare 2007, Colburn 2012, Grover et al 2007, Liu et al 2013, Saviola et al 2007, Shaikh et al 2012.

Intra-articular corticosteroids are not permitted within the 4 weeks preceding randomization. No more than 1 joint per 24-week period may be injected.

No single injection should exceed 40 mg of triamcinolone (or equivalent) and the total dose of intra-articular corticosteroid may not exceed 80 mg of triamcinolone (or equivalent) during any 24-week period.

5.1.2.4 Non-steroidal anti-inflammatory drugs (NSAIDs) (including COX-1 or COX-2 inhibitors), low strength opioids and acetaminophen/ paracetamol

Patients on regular use of NSAIDs (including cyclo-oxygenase 1 (COX-1) or cyclo-oxygenase 2 (COX-2) inhibitors), low strength opioids, or paracetamol/acetaminophen as required should be on stable dose for at least 2 weeks before randomization to allow inclusion.

Changes in NSAID concomitant therapy is permitted for rescue therapy as per the Investigator's clinical judgment and following failure of previously authorized rescue medication (i.e. if low strength opioids or paracetamol/acetaminophen are not successful).

Any change of the NSAIDs, low strength opioids, or paracetamol/acetaminophen treatment during the trial should be recorded on the corresponding eCRF page.

5.2 Treatment arms

At Baseline, patients whose eligibility is confirmed will be randomized in 1:1 ratio in a double-blinded fashion to one of 2 treatment groups (secukinumab: placebo).

Additional study treatments (non-biologic DMARDs including MTX, systemic corticosteroids, and NSAIDs, low strength opioids, or paracetamol/acetaminophen) permitted for use alongside secukinumab in this study are described in Section 5.1.2.

During the study, the study treatment (secukinumab 150 mg and 300 mg, and placebo) provided as PFSs will be self-administered s.c. by the patient at the study center during Treatment Period 1 and Treatment Period 2 under supervision of the Investigator/ qualified study center staff; and at home at Week 28, 32, 40, 44, and 48 (during the Extension Period) as indicated in Table 6-1 and Table 6-2 and described in Section 5.5.4.

5.2.1 Group 1: secukinumab double-blind followed by secukinumab open-label from Week 12

Period 1 – Baseline to Week 12

- secukinumab (150 mg s.c. or 300 mg s.c. depending on severity of skin lesions[1, 2])
  - secukinumab 150 mg (1.0 mL PFS of 150 mg dose) and placebo (1.0 mL PFS) administered at Baseline, Weeks 1, 2 and 3, followed by 4-weekly dosing at Week 4 and Week 8.
  - secukinumab 300 mg (2 × 1.0 mL PFSs of 150 mg dose) administered at Baseline, Weeks 1, 2 and 3, followed by 4-weekly dosing at Week 4 and Week 8.

1. Secukinumab 150 mg will be administered to patients with PsA with BSA ≤ 10% as assessed by PASI (Section 6.4.5), corresponding to mild psoriatic skin lesions).
2. Secukinumab 300 mg s.c. will be administered to patients with PsA (BSA > 10% as assessed by PASI (Section 6.4.5), corresponding to moderate-to-severe psoriatic skin lesions).

Period 2 – Week 12 to Week 24

- secukinumab at the same dose as administered in Period 1 (150 mg s.c. or 300 mg s.c.)
  - secukinumab 150 mg (1.0 mL PFS of 150 mg dose) administered every 4 weeks starting from Week 12 (i.e. at Week 12, 16 and 20).
  - secukinumab 300 mg (2 × 1.0 mL PFSs of 150 mg dose) administered every 4 weeks starting from Week 12 (i.e. at Week 12, 16 and 20).

Period 3 – Week 24 to Week 52

- secukinumab at the same dose as administered in Period 1 and Period 2 (150 mg s.c. or 300 mg s.c.)
  - secukinumab 150 mg (1.0 mL PFS of 150 mg dose) administered every 4 weeks starting from Week 24 (i.e. at Week 24, 28, 32, 36, 40, 44, 48 and 52).
  - secukinumab 300 mg (2 × 1.0 mL PFSs of 150 mg dose) administered every 4 weeks starting from Week 24 (i.e. at Week 24, 28, 32, 36, 40, 44, 48 and 52).

Note: At Week 24, patients who do not reach at least a 20% improvement in TJC and SJC compared to Baseline with secukinumab (150 mg or 300 mg) will be withdrawn from the study.

5.2.2 Group 2: placebo followed by secukinumab from Week 12

Period 1 – Baseline to Week 12

- placebo (2 × 1.0 mL PFSs) administered at Baseline, Week 1, 2 and 3, followed by dosing every 4 weeks starting from Week 4 (i.e. at Week 4 and Week 8)

Period 2 – Week 12 to Week 24

- secukinumab (150 mg s.c. or 300 mg s.c. depending on severity of skin lesions [1, 2])
  - secukinumab 150 mg (1.0 mL PFS of 150 mg dose) administered open-label every 4 weeks starting from Week 12 (i.e. at Week 12, 16 and 20).
  - secukinumab 300 mg (2 × 1.0 mL PFSs of 150 mg dose) administered open-label every 4 weeks starting from Week 12 (i.e. at Week 12, 16 and 20).

1. Secukinumab 150 mg will be administered to patients with PsA (BSA ≤ 10% as assessed by PASI (Section 6.4.5), corresponding to mild psoriatic skin lesions).
2. Secukinumab 300 mg s.c. will be administered to patients with PsA (BSA > 10% as assessed by PASI (Section 6.4.5), corresponding to moderate-to-severe psoriatic skin lesions).

Period 3 – Week 24 to Week 52

- secukinumab open-label at the same dose as administered in Period 2 (150 mg s.c. or 300 mg s.c.)
  - secukinumab 150 mg (1.0 mL PFS of 150 mg dose) continued open-label every 4 weeks starting from Week 24 (i.e. at Week 24, 28, 32, 36, 40, 44, 48 and 52).
  - secukinumab 300 mg (2 × 1.0 mL PFSs of 150 mg dose) continued open-label every 4 weeks starting from Week 24 (i.e. at Week 24, 28, 32, 36, 40, 44, 48 and 52).

Note: At Week 24, patients who do not reach at least a 20% improvement in TJC and SJC compared to Baseline with secukinumab (150 mg or 300 mg) will be withdrawn from the study.

5.3 Treatment assignment, randomization

At Baseline (Visit 2), all eligible patients will be randomized equally via the IRT system to one of the 2 treatment groups (secukinumab or placebo). Within the secukinumab group, patients will be assigned 150 mg or 300 mg based in accordance with the severity of their lesions as described in Section 3.1 and Section 5.2.

The Investigator or his/her designated unblinded qualified site staff will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria.

The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the site staff.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and Investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

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

5.4 Treatment blinding

This study consists of a 12-week double-blind period followed by a 12-week open-label period and a 6-month open-label extension period.

Patients, study center personnel (excluding the unblinded pharmacist/nurse) and data analysts will remain blinded to the identity of the study treatment from the time of randomization until Week 12 using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the exception of the bioanalyst and an independent, unblinded pharmacist/nurse or authorized personnel at the investigator's site who will prepare the study treatment (already provided as PFSs) for the patients.
2. The identity of the secukinumab/placebo treatments will be concealed by the use of study treatments in form of PFSs for s.c. injection filled with secukinumab or placebo that are identical in appearance.

The independent, unblinded pharmacist/nurse or authorized personnel will make sure that no other person will have access to the study treatment or study drug administration documentation.

The bioanalyst will have access to the randomization list to facilitate analysis of the immunogenicity samples (i.e. to avoid the unnecessary analysis of placebo samples).

The independent, unblinded pharmacist/nurse or authorized personnel will contact the IRT after randomization to receive the treatment assignment information. He/she will then prepare the study treatment, which will already have been supplied as PFSs. The independent, unblinded pharmacist/nurse or authorized personnel will contact the IRT again at each visit between Visit 2 (Baseline) and Visit 13 (Week 52) to get the treatment assignment information for the patient.

Starting at Week 12 (end of Treatment Period 1/start of Treatment Period 2) patients will receive secukinumab (150 mg or 300 mg) in an open-label fashion. Patients, data analysts, and study center personnel will be unblinded to the study treatment patients will receive from Week 12. The Clinical Investigator and the site team will be trained during the site initiation visit and the Investigator Meeting to avoid discussing the treatment assigned to the patient with the Ultrasonography Investigator. This will be done despite opening the blind to ensure that the PDUS assessment will be performed without knowledge of current clinical symptoms of the patient.

A Week 24 analysis will be performed after all patients complete the Week 24 visit (see Section 9.6). The data analysts are not blinded after the Week 12 database lock/analyses (as unblinding will have occurred at Week 12 as described above). However, site personnel including the Ultrasonography Investigator and Clinical Investigator will be blinded to the original randomized treatment assignment at randomization (i.e. Baseline to Week 12) until the final database lock and statistical analysis have been completed. Summary results will be shared internally and externally; however, individual unblinded patient data will not be disclosed.

A final database lock will occur when all patients have completed the study (i.e. after the last patient has completed the Week 64/End of Study visit or early withdrawal visit). After the final analysis has been conducted, patient level data including treatment group assignment can be shared. At that time, the Ultrasonography Investigator and Clinical Investigator will be unblinded to the treatment groups.

5.5 Treating the patient

5.5.1 Patient numbering

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

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

If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Period Disposition eCRF.

Patients may be re-screened once and will receive a new Patient Number after they have been re-consented. Patients who are mis-randomized cannot be re-screened.

5.5.2 Dispensing the investigational treatment

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

The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of the label, which corresponds to the placebo or active (secukinumab 150 mg or 300 mg) treatment. Investigator staff (i.e. designated unblinded qualified site staff) will identify the investigational treatment packages to dispense to the patient by contacting the IRT and obtaining the medication numbers. Immediately before dispensing the package to the patient, Investigator staff (i.e. designated unblinded qualified site staff) will detach the outer part of the label from the packaging and affix it to the respective source document (Drug Label Form) for that patient.

At the study visits preceding home study drug administration (i.e. Week 24 and Week 36) the Investigator will dispense, supported by the IRT system, an appropriate number of study drug packages for home administration at Week 28, 32, 40, 44 and 48 (Table 6-2). The Investigator will detach the outer part of the label from the packaging and affix it to the respective source document (Drug Label Form) for that patient. Detailed instructions on the self-administration of the study treatment will be described in the Instructions for Use (IFU) provided to each patient and made available to the site staff and Investigator. These instructions should be reviewed in detail by the patient and the site personnel.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. The Investigator should educate the patient on how to properly store the study treatment when the patient is self-administering at home.

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 each country. They will include storage conditions for the investigational treatment but no information about the patient except for the medication number.

The PFSs (150 mg active/placebo) sealed in their outer box must be stored in an access-controlled/ locked refrigerator between 2°C and 8°C (36°F and 46°F) (Do Not Freeze) and protected from light. They must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

The Investigator or his/her designated unblinded qualified site staff must maintain an accurate record of the shipment and dispensing of investigational treatment in a Drug Accountability Log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

Patients will be asked to return all unused investigational treatment and packaging at the next site visit, at the end of the study or at the time of discontinuation of study drug. At the conclusion of the study, and as appropriate during the course of the study, the Investigator or designee will return all unused study drug, 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 study center.

Destruction of the unused study drug should be done according to local requirements and after approval by the Novartis Clinical Team.

5.5.3.2 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Study treatment (secukinumab (150 mg and 300 mg) and placebo provided as PFSs) will be self-administered s.c. by the patient throughout the study. The injections scheduled to occur at the study center (as outlined in Table 6-1) will be done by the patient (or caregiver) at the study center, under the supervision of the Investigator or study staff. Administration of study treatment at the study center must occur after the study assessments for the visit have been completed.

The injections not scheduled to occur during a study center visit (as outlined in Table 6-2) will be performed by eligible patients (or caregiver) at their home. Patients will be asked to document all doses and dates of self-administration at home in a self-administration log and are required to return this log to the study center at the visit following home administration. The PFS with the ready-to-use study treatment solution will be provided by the study center staff to the patient. Detailed instructions on the self-administration of the study treatment will be described in the IFU and provided to each patient.

At the Baseline visit, patients will be instructed by the study center staff, utilizing the IFU, on how to self-inject using a PFS. Patients will be asked to raise questions, if they have any, and then to proceed with self-injection. At Visit 3 (Week 1) and for subsequent study visits, patients will be asked to refer to the IFU and to proceed directly with self-injection of the study drug (i.e. no prior retraining) under the supervision of the Investigator/qualified study center staff. However, if the patient is not comfortable self-injecting the study drug, then qualified study center staff (such as study nurse) may administer it for the patient.

At the beginning of the study, the Investigator/qualified study center staff will determine if self-administration is appropriate for the patient, e.g. manual dexterity, ability to follow the secukinumab PFS-IFU. If a patient requires a caregiver to administer study drug, the caregiver should be trained by the Investigator/qualified study center staff. It should be recorded on the Dose Administration Record/eCRF(s) whether the patient self-administered the study treatment at home or at the site. All patients should be trained sufficiently and be comfortable with study drug self-administration before the first home administration visit (i.e. before Week 28, Table 6-2). Patients will be instructed to contract the Investigator/study center staff in case of any issue during study drug home administration.

All study drug kits assigned to the patient during the study will be recorded in the IRT.

The first study drug administration will occur at the Baseline/randomization visit only after eligibility criteria have been confirmed, all study-scheduled Baseline assessments have been performed and the scheduled blood samples have been drawn.

At each subsequent visit, all study assessments (as per Table 6-1) should be completed prior to the self-injection of the study drug.

The Investigator should 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. The patient should be instructed to contact the Investigator if he/she is unable for any reason to attend a study visit as scheduled or if he/she is unable for any reason to take the study drug as prescribed.

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

Prior to, and following, self-administration at home, patients should be instructed to contact the Investigator/ study center staff in case they are experiencing any AEs/SAEs or have any concerns.

5.5.4.1 Subcutaneous administration with prefilled syringes

Secukinumab solution for s.c. injection (150 mg in 1.0 mL active/placebo) will be provided in PFSs. The study drug solution must be injected into **non-affected** areas of the skin.

Patients will be instructed by the study center staff on how to self-inject study drug using a PFS, following the IFU. The injections will be self-administered into the appropriate site of the body (thighs, arms, abdomen), and each injection should be given at a different injection site to reduce the risk of reaction. Each new injection should be given at least one inch from the previously used site. If the patient chooses the abdomen, a 2-inch area around the navel should be avoided. The study drug should not be injected into areas where the skin is tender, bruised, red, or hard, or where the patient has scars or stretch marks.

Single PFSs will be packaged in individual boxes. The boxes containing the PFSs with study drug solution should be kept at 2 to 8°C (36°F and 46°F) (Do Not Freeze) and protected from light. Prior to administration the boxes containing the PFSs with study drug solution should be allowed to come to room temperature **unopened** for 15 to 30 minutes prior to injection. Used PFSs should be disposed immediately after use in a sharps container OR according to the regulatory needs of the respective countries.

Any PFS for which a defect or malfunction is noticed prior to or during the injection at any of the study visits, must be kept at the study center until guidance is received from Novartis on whether it should be returned to Novartis for investigation or discarded. Devices identified as defective should be stored according to local guidelines, until specific instruction is discussed with Novartis personnel. Additionally, from Baseline onwards, any noticed defect, malfunction, problem during the injections or product complaints with the PFS should be recorded in the source document and the Use of Device eCRF. Study centers should detail the issue, the date, the kit number and the visit number. Study centers will be asked to record based on their judgment whether the observed issue was primarily related to the device or to the user. Device malfunctions should also be immediately reported to Novartis personnel as a necessary replacement kit may need to be provided.

5.5.5 Permitted dose adjustments and interruptions of study treatment

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

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

The effect of secukinumab on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. In case a live vaccine has been administered due to a medical urgency, the study drug should be interrupted for 12 weeks.

Any study drug interruption must be recorded on the corresponding eCRF page.

5.5.6 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.

If, despite concomitant medication, the patient presents with worsening of disease or does not seem to benefit from study treatment, necessary rescue medication with low strength opioids or paracetamol/acetaminophen is permitted for use alongside secukinumab prior to completion of Week 24 assessments. In addition, changes in NSAID concomitant therapy are permitted prior to Week 24 assessments as per the Investigator's clinical judgment and following failure of previously authorized rescue medication (i.e. if low strength opioids or paracetamol/acetaminophen are not successful).

If there is no patient improvement despite authorized rescue medication and there is a need to use prohibited treatments (as described in Table 5-2) prior to completion of Week 24 assessments, patients will be discontinued from the study and enter into the follow-up period after completing Week 24/early withdrawal visit assessments. Efficacy will be assessed in detail at every study visit, and patients who are deemed not to be benefiting from the study treatment based upon safety and efficacy assessments by the Investigator or for any reason on their own accord will be free to discontinue participation in the study at any time.

Please refer to Section 5.1.2 for details of the additional treatments (non-biologic DMARDs including MTX, systemic corticosteroids, and NSAIDs, low strength opioids, or paracetamol/acetaminophen) permitted for use alongside secukinumab in this study. Please refer to Section 5.5.7 for details of concomitant treatment.

Use of rescue medication must be recorded on the appropriate page in the eCRF.

5.5.7 Concomitant treatment

The Investigator should instruct the patient to notify the study site about any new medications (including over the counter drugs, supplements (such vitamins and calcium), and herbal medications) he/she takes after the patient was enrolled into the study. All medications,

procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded.

Please refer to Section 5.1.2 for details of the additional treatments (non-biologic DMARDs including MTX, systemic, intra articular corticosteroids, and NSAIDs, paracetamol/ acetaminophen and low strength opioids) permitted for use alongside secukinumab in this study.

Changes in NSAID concomitant therapy are permitted prior to Week 24 assessments as a rescue therapy as per the Investigator's clinical judgment and following failure of previously authorized rescue medication (i.e. if low strength opioids or paracetamol/acetaminophen are not successful). Changes in NSAID concomitant therapy after Week 24 assessments are permitted as per the Investigator's clinical judgment. After Week 24, the dose and regimen of other concomitant medications may also be adjusted slowly at the Investigator's discretion and recorded appropriately on the CRF page.

5.5.8 Prohibited Treatment

Use of the treatments displayed in Table 5-2 is NOT allowed after the start of the washout period unless otherwise specified below. Live vaccines should not be given until 12 weeks after the last study drug administration.

Table 5-2 Prohibited treatment

Prohibited treatments	Washout period (before randomization)
Biological immunomodulating agents	never
Etanercept[1]	never
Infliximab[1]	never
Adalimumab, golimumab, certolizumab[1]	never
Ustekinumab, apremilast[1]	never
DMARD (except MTX)	4 weeks
Leflunomide	8 weeks
Leflunomide with cholestyramine washout	4 weeks
Unstable dose of NSAIDs† (COX1 or COX2 inhibitors) (until Week 24 unless rescue therapy is needed)[2]	2 weeks
Analgesics other than NSAIDs, paracetamol/acetaminophen and low strength opioids PRN	2 weeks
Systemic corticosteroids > 10 mg prednisone equivalent[3] (until Week 24)	2 weeks
Unstable dose of systemic corticosteroids ≤ 10 mg prednisone equivalent (until Week 24)	2 weeks
Intra-articular injections[3]	4 weeks
Intramuscular or intravenous corticosteroid treatment	4 weeks
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Live vaccinations	6 weeks
Oral or topical retinoids	4 weeks

Prohibited treatments	Washout period (before randomization)
Photochemotherapy (e.g. PUVA)	4 weeks
Phototherapy (UVA or UVB)	2 weeks
Topical skin treatments (except in face, eyes, scalp and genital area during Screening, only corticosteroids with mild to moderate potency)	2 weeks

Abbreviations: COX: cyclo-oxygenase, DMARD: disease modifying anti-rheumatic drug, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, PRN: pro re nata (as needed); PUVA: psoralen and ultraviolet A; TNFα: tumor necrosis factor alpha; UVA: ultraviolet A; UVB: ultraviolet B
† NSAIDs authorized
1 These agents fall under the category of biologic immunomodulators and are prohibited medications. Administration of these agents requires study discontinuation.
2 Changes in NSAID concomitant therapy are permitted before Week 24 assessments as per Investigator's clinical judgment and following failure of previous authorized rescue medication. 3 See details about corticosteroid management in Section 5.1.2.3.

5.5.9 Discontinuation of study treatment

Study drug must be discontinued if the Investigator determines that continuation of study drug would result in a significant safety risk for a patient.

The following circumstances **require** study drug discontinuation:

- Withdrawal of informed consent.
- Emergence of the following AEs:
  a. Any severe AE or SAE that is not compatible with administration of study medication, including AEs that require treatment with an unacceptable co-medication.
  b. Onset of lymphoproliferative disease or any malignancy except for treated basal cell carcinoma, treated actinic keratoses, treated in situ carcinoma of the cervix or non-invasive malignant colon polyps, which are being or have been removed.
  c. Life-threatening infection.
  d. 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 (general guidance on clinically notable laboratory values is provided in Appendix 1).
- Pregnancy.
- Use of any biologic immunomodulating agent except secukinumab.
- Any protocol deviation that results in a significant risk to the patient's safety.

In addition to these requirements for study drug discontinuation, the Investigator should discontinue study drug for a given patient if there is a lack of improvement or worsening of their symptoms, or if on balance, he/she thinks that continuation would be detrimental to the patient's well-being. The Investigator should discontinue from study drug patients who have < 20% improvement from Baseline in either TJC or SJC at Week 24.

For any patient whose treatment code has been broken inadvertently for any reason the appropriate personnel from the site and Novartis will assess whether study drug should be

discontinued. The Investigator must also contact the IRT to register the patient's discontinuation from study drug.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the Investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the appropriate Study Phase Completion eCRF.

For patients who prematurely discontinue or withdraw during a specific treatment period, the Investigator should ensure that the patient completes an End of Study visit (corresponding to the last visit for the current period of treatment, e.g. Week 12, 24 and 52) and also return for a Follow-up visit after 4 weeks of last treatment (i.e. Week 56), and 12 weeks after last study treatment (i.e. at Week 64/F64) as indicated in Table 6-1. Even if the patient is not willing to come back for all assessments, every effort should be made to collect the scheduled PDUS assessments. The final visit should be performed before any new treatment is initiated.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study will not be replaced.

5.5.10 Withdrawal of informed consent

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

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

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

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table (Table 6-1).
Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

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

For Europe and Rest of World: 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.

5.5.11 Loss to follow-up

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

5.5.12 Emergency breaking of assigned treatment code

Patients, study center personnel (including the Ultrasonography Investigator, and Clinical Investigator) and data analysts will be fully blinded to the treatment assigned to patients at randomization for the first 12 weeks of the study as described in Section 5.4.

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The Investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Global Trial Lead (GTL) that the code has been broken.

It is the Investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT 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 Investigator will provide protocol number CAIN457F2354, study drug name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case an emergency treatment code break is required at a time when the Investigator and backup are unavailable.

Study drug must be discontinued after emergency unblinding.

5.5.13 Study completion and post-study treatment

A patient will be considered to have completed the study if he/she received a total of 52 weeks of study treatment and upon completion of the scheduled study assessments and procedures up to and including Visit F64.

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 eCRF page. In any case, the Investigator or designated unblinded qualified site staff must contact the IRT as soon as possible to record the patient's study completion (Visit F64) and/or discontinuation.

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. This treatment may be any non-biologic DMARD. In case of a biologic treatment, a waiting period of 3 months before initiating the treatment is recommended.

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as a prematurely withdrawn patient as described in Section 6. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) of the early termination of the trial. In the Netherlands only, the Investigator will be responsible for informing the METc in case of early termination of the trial.

5.5.15 End of study

The end of study will occur when the last patient has completed their last visit (i.e. Week 64 or early withdrawal visit) in the study.

In the Netherlands, the end date of the study will be reported to the METc within 90 days of study end date.

6 Visit schedule and assessments

During the period of the study from Screening to Follow-up Week 64 (F64), the assessments must be performed as indicated in Table 6-1.

Patients should be seen for all visits on the designated day or as closely as possible to the original planned visit schedule.

- For visits scheduled through Week 4, the study treatment should not be administered less than 4 days from the previous administration.
- For visits scheduled after Week 4, the study treatment should not be administered less than 14 days from the previous administration.
- A visit window of ± 3 days must be observed for visits with PDUS assessments scheduled from Baseline through to the end of study.

Patients who prematurely discontinue during a specific treatment period should return for the final visit within that treatment period (4 weeks after the last study treatment), as well as return for the follow-up visit (Week F64) 12 weeks after the last study treatment.

If patients refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the reason. Documentation of attempts to contact the patient should be recorded in the source documentation.

Table 6-1 Assessment schedule

	Screening Period	Treatment Period 1							Treatment Period 2			Extension Period		Follow-up	
Week	**-1 to -4 to BSL**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12[4]**	**16**	**20**	**24†[7] TD/ PSW**	**36**	**52**	**56†[7] TD/ PSW**	**F64[7] TD/ PSW**
Visit No.	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Informed consent	X										X				
Inclusion/exclusion criteria	X	X													
Relevant medical history/ current medical condition	X														
Smoking history	X														
Cardiovascular medical history	X														
Demography	X														
Psoriasis/PsA medical history and previous therapies	X														
CASPAR criteria	X														
Physical examination[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X														
Weight	X	X						X			X			X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPD skin test[2] or QuantiFERON TB-Gold test	X														
Chest X-ray / MRI[3]	X														
Randomization via IRT		X													
IRT contact such as for registration or drug supply including home administration.	X	X	X	X	X	X	X	X	X	X	X	X	X		
Administration of s.c. study treatment via PFS at study site[4] (see Table 6-2 for timing of home		X	X	X	X	X	X	X[4]	X	X	X[#]	X	X		

	Screening Period	Treatment Period 1							Treatment Period 2			Extension Period		Follow-up	
Week	**-1 to -4 to BSL**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12[4]**	**16**	**20**	**24†[7] TD/ PSW**	**36**	**52**	**56†[7] TD/ PSW**	**F64[7] TD/ PSW**
Visit No.	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
administrations)															
Check self-administration log for home administration												X	X		
Prior/concomitant medication/ non-drug therapy	X	Update as needed													
AEs/SAEs[5] (incl. injection site reaction & occurrence of infections)	X	Update as needed													
Hematology, blood chemistry, urinalysis	X	X				X		X			X	X	X	X	
Hepatitis B, C or HIV serology** (only in countries where required)**	S	S													
Serum pregnancy test	X														
Urine pregnancy test[6]		X				X		X	X		X	X	X	X	
Immunogenicity		X						X			X		X		X
Pharmacokinetic assessments		X						X			X		X		X
Antinuclear antibodies (ANA)		X						X			X		X		X
Anti-dsDNA		X						X			X		X		X
Anti-CCP	X														
Rheumatoid factor (RF)	X														
High sensitivity C-reactive protein (hsCRP)	X	X	X	X		X	X	X	X	X	X	X	X	X	X
PDUS of affected joints out of 48*	X	X	X	X		X	X	X	X	X	X	X	X		
PDUS of enthesitis sites out of 5 entheses*	X	X	X	X		X	X	X	X	X	X	X	X		
[redacted]															

	Screening Period	Treatment Period 1							Treatment Period 2			Extension Period		Follow-up	
Week	**-1 to -4 to BSL**	**BSL**	**1**	**2**	**3**	**4**	**8**	**12[4]**	**16**	**20**	**24†[7] TD/ PSW**	**36**	**52**	**56†[7] TD/ PSW**	**F64[7] TD/ PSW**
Visit No.	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
[redacted]															
Leeds Dactylitis Index	X	X	X	X		X	X	X	X	X	X	X	X		
Tender and swollen joint counts (TJC 78, SJC 76)	X	X	X	X		X	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	X	
Patient's global assessment of disease activity (VAS)		X	X	X		X	X	X	X	X	X	X	X	X	
SPARCC	X	X	X	X		X	X	X	X	X	X	X	X	X	
Physician's global assessment of disease activity (VAS)		X	X	X		X	X	X	X	X	X	X	X	X	
Health assessment questionnaire (HAQ-DI©)		X	X	X		X	X	X	X	X	X	X	X	X	
PASI scoring (only if ≥ 3% of BSA at BSL or after)		X	X	X		X	X	X	X	X	X	X	X	X	
Treatment period 1 completion form								X							
Treatment period 2 completion form											X				
Treatment period 3 completion form													X		
Follow-up completion form															X

Abbreviations:

AE: adverse event, anti-CCP: anti-cyclic citrullinated peptide, BSA: body surface area, BSL: baseline, CASPAR: Classification of psoriatic arthritis, HAQ-DI©: Health assessment questionnaire-disability index, HIV: human immunodeficiency virus, hsCRP: high sensitivity C-reactive protein,

IRT: interactive response technology, MRI: magnetic resonance imaging, PDUS: power Doppler ultrasound, PFS: prefilled syringe, PPD: purified protein derivative, PsA: psoriatic arthritis, PSW: premature subject withdrawal, RF: rheumatoid factor, SAE: serious adverse event, SJC: swollen joint count, SPARCC: Spondyloarthritis Research Consortium of Canada, TD: study treatment discontinuation, TJC: tender joint count, VAS: visual analog scale.

[redacted]

** Hepatitis B and/or hepatitis C and/or HIV serology testing to be performed during screening period only if required as per local medical practice or local regulations prior to initiation of therapy. These assessments will be documented in source records only and will not be entered into the eCRF.

* A visit window of ± 3 days must be observed for PDUS assessments scheduled from Baseline to the end of study.

Note: this study consists of 3 treatment periods: Period 1 (Baseline to Week 12), Period 2 (Week 12 to Week 24) and Period 3 (Week 24 to Week 52)

1 These assessments are source documentation only and will not be entered into the eCRF.

2 The PPD skin test can be performed at any time during the Screening period but it has to be read within 72 hours and before randomization.

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

4 All patients will be assigned to open-label secukinumab from Week 12:

Patients in Group 1 (secukinumab 150 mg or 300 mg) will continue to receive the same dose every 4 weeks but in an open-label fashion (with no placebo injections for patients assigned secukinumab 150 mg) starting from Week 12.

Patients assigned to Group 2 (placebo) at randomization will switch to open-label secukinumab treatment (150 mg or 300 mg s.c.) starting from Week 12; secukinumab dosing will be every 4 weeks starting from Week 12 (with no loading dose).

5 AEs /SAEs that occur after the patient has signed the informed consent (including those that occur during home administration of study drug) must be captured on the appropriate eCRF page. Any AEs that are treatment-emergent should be reported until 12 weeks after the last study treatment..

6 Kits will be provided by the central laboratory and tests will be performed locally.

7 These assessments are also to be conducted for patients who discontinue.

† Patients who prematurely discontinue during Treatment Period 1 should return for assessments associated with Week 12 visit (4 weeks after the last study treatment in Treatment Period 1) and the final follow-up visit (Week F64) 12 weeks after the last study treatment.

† Patients who prematurely discontinue during Treatment Period 2 should return and complete assessments associated with Week 24 visit (4 weeks after the last study treatment in Treatment Period 2) and the final follow-up visit (Week F64) 12 weeks after the last study treatment.

† Patients who prematurely discontinue during the Extension Period should return for assessments associated with the Week 56 visit (4 weeks after the last study treatment) and the final follow-up visit (Week F64) 12 weeks after the last study treatment.

The dose at Week 24 will be administered only if the patient signs the ICF for participating in the Extension Treatment period of the study.

Table 6-2 Overview of study drug administration

	Treatment Period 1							Treatment Period 2			Extension period						
Week	**BSL**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Study visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			**12**				**13**
Study drug administration																	
All Groups	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**H**	**H**	**S**	**H**	**H**	**H**	**S**

Abbreviations: BSL = baseline, H = home administration; S = administration at study center

6.1 Information to be collected on screening failures

All patients who have signed informed consent but who are not entered into the treatment period will have the study completion page for the Screening period, demographics, inclusion/exclusion, and SAE data collected. Adverse events that are not SAEs will be followed by the Investigator and collected only in the source data. The reason for screening failure will be recorded in the CRF.

6.2 Patient demographics/other baseline characteristics

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

- Date of birth, age, sex, race, ethnicity and source of patient referral.
- Relevant PsA/psoriasis and general medical history/current medical condition data until the start of study drug, such as date of diagnosis of PsA/psoriasis, previous PsA/psoriasis therapies, BSA, severity of skin lesions, cardiovascular medical history, and smoking history. The SPARCC will be assessed at both the Screening and Baseline Visit.

Whenever possible, diagnoses and not symptoms will be recorded.

6.3 Treatment exposure and compliance

All doses of study drug administered will be recorded on the appropriate Dosage Administration Record eCRF page by the designated unblinded qualified site staff. Study drug doses and corresponding dates of self-administration at home should be documented by the patient in a self-administration log. Patients are required to return the self-administration log as well as all dispensed study drug material at every visit back to the study center for a compliance check.

Patient compliance to the study drug should be assessed by qualified site personnel at each study visit using the study kits and documentation regarding study drug dispensation and administration. Compliance will also be assessed continuously during the conduct of the study by Novartis study personnel using medication kits and corresponding documentation.

6.4 Efficacy

The efficacy outcome measures used in this study are as follows:

- OMERACT/EULAR global synovitis score and its components
- OMERACT enthesitis score and its morphological components
- American College of Rheumatology (ACR) 20, 50 and 70 responses
- Spondyloarthritis Research Consortium of Canada (SPARCC)
- Swollen joint count (SJC)/Tender joint count (TJC)
- Patient's global assessment of disease activity (Visual Analog Scale (VAS))
- Physician's global assessment (PGA) of disease activity (VAS)
- Patient's assessment of PsA pain intensity (VAS)
- Health assessment questionnaire – disability index (HAQ-DI©)

- Minimal disease activity (MDA)
- Psoriasis area and severity index (PASI)

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

6.4.1 Power Doppler Ultrasonography

PDUS evaluation will be performed at each joint site out of 48 and at each enthesis site out of 5 entheses by an independent expert in musculoskeletal ultrasound, who will be blinded to the patient's identity, symptoms and clinical evaluations. The processing settings will be kept constant during the examination and the temperature of the room will be kept stable at 20°C. The PDUS will be performed bilaterally for 24 pairs of joints:

- Metacarpophalangeal (MCP) joints 1 to 5.
- Proximal interphalangeal (PIP) joints 1 to 5.
- Metatarsophalangeal (MTP) joints 1 to 5.
- Wrist, elbow, shoulder (glenohumeral), knee, and ankle (tibiotalar).
- Distal interphalangeal (DIP) 2 to 5.

The PDUS assessment will consist of an evaluation of hypoechoic synovial hyperplasia (SH) and joint effusion (JE) using Grayscale and synovial vascularization using Power Doppler. The pre-specified set of 24 paired joints will be scanned at each visit from the dorsal aspect with the joint in a neutral position, except for the knee, which will also be examined in a flexed position (30°). Note: only affected joints will be assessed after Visit 2 (Baseline). Standardized joint and probe positions will be used based on a reference atlas, which also show examples of synovitis grading for each site examined. The presence of synovitis (i.e. SH and Power Doppler, without JE) will be scored according to the OMERACT-EULAR PDUS composite semi-quantitative scale (0 to 3) using high resolution PDUS machines as described in Appendix 6 and Appendix 9.

For the enthesis evaluation, ultrasound will be initially performed in B mode to detect morphologic abnormalities, and subsequently with power Doppler to detect abnormal vascularization at bony insertions. The following entheses will be examined bilaterally:

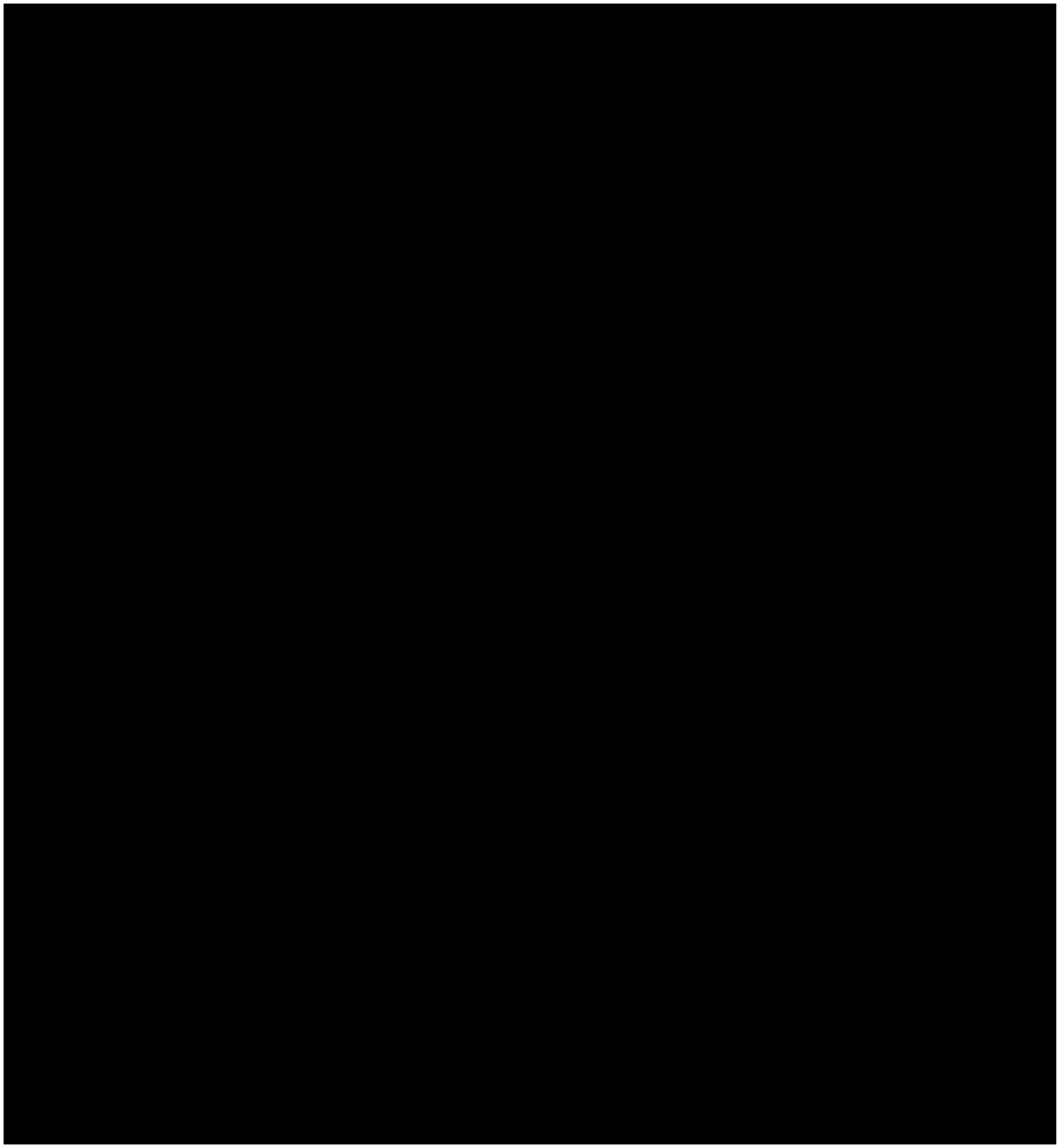
1. Common extensor tendon at its insertion at the lateral humeral epicondyle.
2. Quadriceps tendon at its insertion at the superior pole of the patella.
3. Patellar tendon at its proximal insertion at the inferior pole of the patella.
4. Patellar tendon at its distal insertion at the tibia tuberosity.
5. Calcaneal insertions:
    a. Achilles tendon at its insertion at the calcaneus.
    b. Plantar aponeuroses at its insertion at the calcaneus.

Each affected enthesis out of 5 targeted entheses will be scored in terms of inflammatory and morphological components according to the OMERACT enthesitis composite semi-quantitative scale (0 to 3) as described in Appendix 7.

The total time required for each PDUS assessment of joint inflammation and enthesitis in the study will be recorded in the eCRF in order to evaluate the variability of time spent by ultrasonographers to assess multiple joints and enthesitis across the sites.

Quality control assessment of the scoring will be performed for the first patient included from each center and once all patients have completed the study (i.e. following the last patient's last visit) when the last patient enrolled in the trial has completed their last visit. Please refer to Appendix 6.

The name and type of PDUS machine used will also be recorded in the eCRF. PDUS equipment recommendations are described in Appendix 9.



6.4.2 American College of Rheumatology response

The ACR response (Appendix 4) will be used to determine efficacy (Felson 1995). A patient is defined as e.g. an ACR 20 responder if, and only if, the following 3 conditions hold:

- Patient has a ≥ 20% improvement in the number of tender joints (based on 78 joints).
- Patient has a ≥ 20% improvement in the number of swollen joints (based on 76 joints).
- Patient has a ≥ 20% improvement in 3 of the following 5 domains:
  1. Patient's global assessment of disease activity (measured on a VAS scale, 0-100).
  2. Physician's global assessment of disease activity (measured on a VAS scale, 0-100).
  3. Patient's assessment of PsA pain (measured on a VAS scale, 0-100).
  4. Health Assessment Questionnaire-Disability Index (HAQ-DI©) score.
  5. Acute phase reactant (high-sensitivity C-reactive protein (hsCRP)).

An ACR 50 response is defined as a 50% improvement in at least 3 of the 5 measures and a 50% improvement in the SJC and TJC.

An ACR 70 response is defined as a 70% improvement in at least 3 of the 5 measures and a 70% improvement in the SJC and TJC.

The ACR response is to be assessed at the visits/time points shown in Table 6-1.

6.4.2.1 Swollen joint count/ tender joint count

Joint counts will be performed by the independent assessor (i.e. the Clinical Investigator) who must be well trained and part of the site personnel. Whenever possible, the same evaluator should perform these assessments at all visits. The 78 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 2 first carpometacarpal, 10 MCP, 10 PIP, 8 DIP joints of the hands, the 2 hip, 2 knee, 2 talo-tibial, 2 mid-tarsal, 10 MTP, 10 PIP, and 8 DIP joints of the feet. All of these except for the hips are assessed for swelling. 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 SJC.

Data is recorded for tender and swollen joints (right or left side), i.e. a box (no, yes or not applicable) needs to be ticked for all joints. The total number of tender and swollen joints (right and left) will be automatically calculated in the eCRF. For more information, please refer to Appendix 5.

6.4.2.2 Patient's global assessment of disease activity

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

6.4.2.3 Physician's global assessment of disease activity

The PGA of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question "Considering all the ways the disease affects your patient, draw a line on the scale for how well his or her condition is today." To

enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity when performing his own assessment on that patient.

6.4.2.4 Patient assessment of psoriatic arthritis pain intensity

The patient's assessment of pain will be performed using 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 PsA today".

6.4.2.5 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 (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.

6.4.2.6 High sensitivity C-reactive protein

Blood for this assessment will be obtained in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment. Since the results of this test may unblind study personnel (such as the Ultrasonography Investigator and Clinical Investigator), results from the central laboratory will be provided for Screening and Baseline only. The hsCRP results from samples collected during the treatment period will be revealed following database lock only.

6.4.3 Minimal disease activity

The proportion of patients achieving MDA (Coates 2010) (5 of the 7 following: ≤ 1 TJC, ≤ 1 SJC, PASI ≤ 1 or BSA with PsA < 3%, patient pain VAS ≤ 15, patient global VAS ≤ 20, HAQ-DI© ≤ 0.5, and tender entheseal points ≤ 1).

6.4.4 Spondyloarthritis research consortium of Canada – enthesitis index

The SPARCC (Maksymowych et al 2009) enthesitis index focuses on the clinical evaluation and validation of the 16 sites shown in Table 6-3. SPARCC assessments will be performed as indicated in the schedule of assessments (Table 6-1).

Table 6-3 Entheses sites comprising the total spondyloarthritis research consortium of Canada enthesitis index

Greater trochanter	R/L
Quadriceps tendon insertion into the patella	R/L
Patellar ligament insertion into the patella and tibial tuberosity	R/L
Achilles tendon insertion	R/L
Plantar fascia insertion	R/L
Medial epicondyles	R/L
Lateral epicondyles	R/L
Supraspinatus insertion	R/L

Abbreviations: R = right, L = left
Note: Tenderness at each site is quantified on a dichotomous basis: 0= non-tender and 1= tender.
Range of scores: 0 to 16

6.4.5 Psoriasis area and severity index

The percentage BSA affected by psoriatic skin involvement will be performed using PASI for patients at Baseline and Week 12 (as applicable) to assess the dose of secukinumab required. Patients with a BSA ≤ 10% will be assigned secukinumab 150 mg while those with a BSA > 10% will be assigned secukinumab 300 mg as described in Section 5.5.4.

The PASI assessment will be conducted for patients in whom at least 3% of the BSA was affected by psoriatic skin involvement at Baseline. The PASI assesses the extent of psoriasis on 4 body surface areas (head, trunk and upper and lower limbs) and the degree of plaque erythema, scaling and thickness. A PASI score (Fredriksson and Pettersson 1978, Weisman 2003, Gottlieb 2005) will be derived as indicated in Table 6-4. PASI scoring will be conducted during the study for all patients with a BSA ≥ 3% at Baseline and for patients with a BSA ≥ 3% at subsequent visits (i.e. if not ≥ 3% at Baseline).

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:

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

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

PASI =

$$0.1\,(EH+IH+DH)AH + 0.2(EU+IU+DU)AU + 0.3(ET+IT+DT)AT + 0.4(EL+IL+DL)AL$$

The keys for the letters are provided in Table 6-4.

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

Table 6-4 Psoriasis area and severity index 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

6.4.5.1 Definitions of efficacy variables based on psoriasis area and severity index

The following definitions will be used in this study based on the Committee for Medicinal Products for Human Use (CHMP) guidelines for psoriasis (CHMP/EWP/2454/02 corr):

- **PASI 75 response**: patients achieving ≥ 75% improvement (reduction) in PASI score compared to Baseline are defined as PASI 75 responders.
- **PASI 90 response**: patients achieving ≥ 90% improvement (reduction) in PASI score compared to Baseline are defined as PASI 90 responders.

6.4.5.2 Leeds Dactylitis Index (LDI)

The Leeds Dactylitis Index (LDI) (Helliwell 2005) 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. 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 11). This modification is referred to as LDI basic and will be applied in this study. The LDI requires a finger circumference gauge or a tape measure to measure digital circumference.

6.4.6 Appropriateness of efficacy assessments

Power Doppler ultrasound (PDUS), which allows the assessment of both inflammatory changes and structural damage, has been shown to be a valid and reliable tool for evaluating spondyloarthritis enthesitis (de Miguel et al 2009, D'Agostino et al 2011). The use of PDUS for monitoring pathological findings indicative of joint or soft tissue involvement in patients with PsA has already been demonstrated for patients treated with anti-TNFα therapy. This study will evaluate the use of PDUS for assessing the response to secukinumab (150 mg and 300 mg s.c.) in terms of the change in the synovium of target joints and peripheral entheses in patients with moderate-to-severe PsA who have had an IR to non-biologic DMARD therapy. All other efficacy outcome measures used in this study are standard measures used across many PsA trials and are consistent with the measures used in the Phase 3 clinical trials in PsA with secukinumab.

6.5 Safety

Safety assessments will consist of the evaluation of all AEs and SAEs including injection site reactions, physical examination, vital signs and laboratory assessments. An assessment of anti-secukinumab antibody development (immunogenicity) will also be performed.

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

- Incidence and severity of AEs/SAEs.
- Physical examinations.
- Vital signs.
- Height and weight.
- QuantiFERON TB-Gold test or PPD skin test.
- Chest X-Ray or MRI
- Local tolerability (injection site reactions).
- Laboratory evaluations (hematology, clinical chemistry, urinalysis).
- Pregnancy and assessment of fertility.
- Tolerability of secukinumab.
- Immunogenicity.

6.5.1 Physical examination

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

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 AE eCRF.

6.5.2 Vital signs

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

If possible, vital signs assessments should be performed by the same study site staff member using the same validated device throughout the study.

6.5.3 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 scale throughout the study.

6.5.4 QuantiFERON TB-Gold test or PPD skin test

Either a QuantiFERON TB-Gold test or a PPD skin test must be performed at Screening. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis, or if presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.

QuantiFERON TB-Gold test

- A QuantiFERON TB-Gold test is to be performed at the Screening visit and the results to 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.
- The 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.

PPD skin test

A PPD skin test is to be performed at Screening and read before randomization to determine the patient's eligibility for the study. The test dose is bioequivalent to 5 tuberculin units of standard PPD injected intradermally, usually into the volar surface of the forearm. The site is cleaned and the PPD extract is then injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration) will take 48-72 hours to develop, the patients must return to the Investigator's site within that time for a proper evaluation of the injection site. This will determine whether the patient has had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration ≥ 5 mm (or according to local practice/guidelines) is interpreted as a positive result.

6.5.5 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected as 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 1. 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.

6.5.5.1 Hematology

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

6.5.5.2 Clinical chemistry

Serum chemistries will include glucose, urea, creatinine, total bilirubin, AST/SGOT, ALT/SGPT, gamma glutamyl transferase (GGT), alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, and uric acid.

6.5.5.3 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 page.

6.5.5.4 Pregnancy and assessments of fertility

Secukinumab must not be given to pregnant women; therefore effective methods of birth control must be used for women of child-bearing potential (see exclusion criteria definitions, Section 4.2).

A serum β-hCG test will be performed in all women at Visit 1 (Screening). All women of child bearing potential at Screening will have local urine pregnancy tests as indicated in Table 6-1. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued from the trial.

6.5.6 Tolerability of secukinumab

Tolerability will be assessed by AEs, laboratory values, injection site reaction, and immunogenicity (see Section 6.5.8).

6.5.7 Additional parameters

Blood will be obtained at the Screening visit (Visit 1) for anti-CCP antibodies and the Rheumatoid Factor (RF). Antinuclear antibodies (ANA) and anti-dsDNA antibodies will also be assessed at the visits/time points indicated in Table 6-1.

6.5.8 Immunogenicity

Blood samples for immunogenicity (anti-AIN457 antibodies) will be taken pre-dose at the scheduled time points as indicated in Table 6-1.

In addition, if a patient discontinues from the study at any time point, he/she will need to provide a sample at the last visit. The actual sample collection date and exact time will be entered on the Immunogenicity Blood collection eCRF. Sampling problems will be noted in the comment section of the eCRF.

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

A laboratory manual will be provided to Investigators with detailed information on sample collection, handling and shipment.

Tubes and preprinted labels will be provided by the central laboratory to the study centers.

Analytical method

An electrochemiluminescence method will be used for the detection of potential anti-secukinumab antibody formation. The detailed method description to assess immunogenicity will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report.

Table 6-5 Immunogenicity sample log

Week	Immunogenicity Sample Log*
0	301
12	302
24	303
52	304
64	305

* If an IG sample is collected at an unscheduled visit, the sample numbers will follow the pattern: 3001, 3002, etc.

6.5.9 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic in 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 tuberculosis. The radiation exposure that results from the chest X-ray safety measurements are estimated to be far below 1 mS. For effective radiation doses below 3 mS (300 mrem), the risk is considered to be minimal. Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure reliable safety measures before the treatment with a biologic.

6.6 Other assessments

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

6.6.1 Resource utilization

Not applicable.

6.6.2 Pharmacokinetics

Pharmacokinetic samples will be obtained for all patients and the secukinumab concentrations will be assessed in the serum. The PK samples will be collected pre-dose at scheduled visits/ time points as indicated in Table 6-1 and Table 6-6. All blood samples will be drawn by direct venipuncture in a forearm vein. The actual sample collection date and exact time will be entered on the PK blood collection summary eCRF.

Sampling problems will be noted in the comments section of the eCRF.

The bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the PK samples. The bioanalyst will provide the sample concentration data to the team under blinded conditions. The bioanalyst will keep this information confidential until clinical database lock.

Table 6-6 Pharmacokinetic sample log

Week	Timepoint	PK Sample No.*	PK Collection No.
Baseline	0 (pre-dose)	1	1
Week 12	2016 h (pre-dose)	2	1
Week 24	4032 h (pre-dose)	3	1
Week 52	8736 h (pre-dose)	4	1
Week F64	10752 h (anytime)	5	1

* If a PK sample is collected at an unscheduled visit, the sample numbers will follow the pattern: 1001, 1002 etc.

Pharmacokinetic sample handling, labeling and shipment instructions

Laboratory manuals will be provided by the central laboratory with detailed information on sample collection, sample handling and shipment. Tubes and labels will be provided by the central laboratory with study/sample type information pre-printed on the label.

Analytical methods

An ELISA method will be used for bioanalytical analysis of secukinumab in serum, with an anticipated lower limit of quantification (LLOQ) of 80 ng/mL. The detailed method description to assess secukinumab concentration will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR).

6.6.3 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

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

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

The occurrence of AEs should 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, laboratory test, or other assessments.

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

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

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

Adverse events should be recorded in the AE eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information.

- The severity grade
  - Mild: usually transient in nature and generally not interfering with normal activities.
  - Moderate: sufficiently discomforting to interfere with normal activities.
  - Severe: prevents normal activities.
- Its relationship to the study drug (no/yes).

- Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/ not resolved should be reported.
- Whether it constitutes a SAE (see Section 7.2 for definition of SAE).
- Action taken regarding study drug.

All AEs should be treated appropriately. Treatment may include one or more of the following and this should be recorded in the CRF:

- No action taken (i.e. further observation only).
- Study drug dosage adjusted/temporarily interrupted.
- Study drug permanently discontinued due to this ae.
- Concomitant medication given.
- Non-drug therapy given.
- Patient hospitalized/patient's hospitalization prolonged.
- Its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

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

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

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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:

- Is fatal or life-threatening.
- Results in persistent or significant disability/incapacity.
- Constitutes a congenital anomaly/birth defect.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.

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

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

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

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

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

All AEs (serious and non-serious) are captured on the eCRF, SAEs also require individual reporting to the Novartis Drug Safety and Epidemiology (DS&E) Department as per Section 7.2.2.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 12 weeks (84 days) after last administered dose of study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The 12-week follow-up period after final study treatment administration also applies to patients who have been withdrawn from the study early.

Any SAEs experienced after this period should only be reported to Novartis if the Investigator suspects a causal relationship to study drug.

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

Information about all SAEs (either initial or follow up information) is collected and recorded in English on the paper SAE Report Form or the electronic SAE Form within the Oracle Clinical/Remote Data Capture (OC/RDC) system (where available). The Investigator must

assess the relationship to each specific component of the study drug (if the study drug consists of several components).

Serious adverse events (initial and follow-up) that are recorded on the paper SAE form should be faxed within 24 hours of awareness of the SAE to the local Novartis DS&E Department. The telephone and fax number of the contact persons in the local DS&E department, specific to the site, are listed in the Investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the CRF documentation at the study center. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Serious adverse events (initial and follow-up) that are recorded electronically in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis DS&E Department immediately after Investigator signature or 24 hours after entry, whichever occurs first.

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

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

7.2.2.1 Safety reporting specific to the Netherlands

For the Netherlands only, the Sponsor will report the SAEs through the web portal ToetsingOnline to the accredited METc that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the Sponsor has first knowledge of the SAEs.

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following 3 conditions are met:

1. The event must be serious (see Section 7.2.1);
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:

- Summary of Product Characteristics for an authorized medicinal product;
- Investigator's Brochure for an unauthorized medicinal product.

For the Netherlands only, the Sponsor will report expedited the following SUSARs to the METc:

- SUSARs that have arisen in the clinical trial that was assessed by the METc;
- SUSARs that have arisen in other clinical trials of the same Sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METc.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METc. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the Competent Authority.

The Sponsor will expedite reports of all SUSARs to the Competent Authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the Sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

In addition to the expedited reporting of SUSARs, the Sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METc, Competent Authority, and Competent Authorities of the concerned Member States.

This safety report consists of:

- A list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- A report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

7.3 Liver safety monitoring

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

The following 2 categories of abnormalities/AEs have to be considered during the course of the study:

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

Please refer to Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Appendix 2 should be followed up by the Investigator or designated personal at the study center as summarized below:

Detailed information is outlined in Appendix 2.

For the liver laboratory trigger:

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

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

For the liver events:

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

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

7.4 Renal safety monitoring

There has been no safety signal for nephrotoxicity with secukinumab to date in approximately 13000 patients and healthy patients exposed (cut-off date 25-Jun-2018, DSUR No. 008), and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney. All patients with laboratory tests containing clinically significant abnormal values (see Appendix 1 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment-related AE, is defined. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals; however, no special measures for renal safety monitoring are planned.

7.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

See Table 7-1 for guidance on capturing the study treatment errors including misuse/abuse.

Table 7-1 Treatment error types

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

AE=adverse event, eCRF=electronic case report form, DAR=dose administration record, SAE=serious adverse event

7.6 Pregnancy reporting

All pre-menopausal women who are not surgically sterile will have a urine pregnancy test. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

To ensure patient safety, each pregnancy occurring while the patient is on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The study drug must be discontinued, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments.

Pregnancy should be recorded on the Pharmacovigilance Pregnancy Form and reported by the Investigator to the local Novartis DS&E Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug. Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on the SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis representative will review the protocol and CRFs with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the study center data. The field monitor will visit the study center to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to

ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each study center's data may be performed by a centralized Novartis Clinical Research Associate organization. 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 study 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 informed consent form signed by the patient (a signed copy is given to the patient).

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

8.2 Data collection

Designated Investigator staff will enter the data required by the protocol into the OC/RDC system. Designated Investigator center staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated Investigator center staff.

The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the Investigator will receive copies of the patient data for archiving at the study center.

8.3 Database management and quality control

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

Concomitant medications entered into the database will be coded using the World Health Organization Drug Reference List, which employs the Anatomical Therapeutic Chemical

classification system. Concomitant procedures, non-drug therapies and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using the Novartis IRT system. Novartis will also manage the database.

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

8.4 Scientific Committee

A Scientific Committee has been instituted for this study based on member affiliations to the OMERACT group and expertise in PDUS and methodology:

- [redacted], France, Principal Investigator for the study.
- [redacted], Netherlands

8.5 Data Monitoring Committee

In alignment with the EMA Guideline on Data Monitoring Committees (DMCs) (EMEA/CHMP/EWP/5872/03 Corr) no DMC is deemed to be required for this Phase IIIb clinical study. A pharmacovigilance review concluded that substantial amount of safety data for the study drugs have been collected through all study phases and that a DMC would not be beneficial for the study. Furthermore, the study population is not considered to have an elevated risk of more severe outcomes during this study, which is also in accordance with US Department of Health and Human Services FDA guidelines (Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006).

9 Data analysis

Summary statistics for continuous variables include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. For binary or discrete variables the absolute number of patients in each category and relative frequencies will be provided.

Unless otherwise specified, p-values will be presented as 1-sided p-values and the type I error rate (alpha) will be 5%.

Inferential efficacy comparisons with placebo will generally focus on the first 12 weeks of treatment. Efficacy and safety data for the placebo-controlled period (or the entire treatment period as appropriate) will be presented by study treatment groups.

Note that the study treatment groups for a patient may differ depending on the time period of the analysis and whether the patient is assessed for efficacy or safety.

Data may also be presented by a combination of the ‘comparative’ and ‘open-label’ study treatment groups.

These study treatment groups represent the treatment combinations the patients experience over the course of the entire trial.

9.1 Analysis sets

Randomized set: The randomized set will be defined as all patients who were randomized.

Unless otherwise specified, mis-randomized patients will be excluded from the randomized set. Mis-randomized patients are defined as those patients who were mistakenly randomized prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized patients are treated as screen failures.

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

Safety set: The Safety set will include all patients who took at least 1 dose of study treatment during the treatment period. Patients will be evaluated according to study treatment received.

9.2 Patient demographics and other baseline characteristics

Demographics and baseline characteristics

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

Baseline comparability of the randomized study treatment groups will be assessed through descriptive methods for the demographic variables indicated in the schedule of assessments (Table 6-1) including:

- Sex, age, race, ethnicity, weight, height, BMI and smoking history.

Baseline disease characteristics will also be compared for the variables indicated in the schedule of assessments (Table 6-1) including:

- Time since first diagnosis of PsA, type and dose of DMARDs at randomization, Global PDUS, PASI, SPARCC enthesitis index and ACR components.

The QuantiFERON TB-Gold test or PPD skin test (depending on local guidelines), anti-CCP antibodies, chest X-ray or MRI and the RF will be summarized at Screening.

Medical history

Any significant prior or active medical condition at the time of signing informed consent will be coded using MedDRA. These medical conditions will be summarized by primary system organ class and preferred term. Psoriatic arthritis history and psoriasis history will be summarized separately by pre-specified categories recorded on the eCRF.

To establish a baseline level of cardiovascular risk, the number and percentage of patients with pre-solicited cardiovascular risk factors will be summarized by treatment group. The number of cardiovascular risk factors that each patient has will also be summarized by treatment group. If it is unknown whether or not a patient currently or previously experienced

a specific cardiovascular risk factor, it will be assumed that cardiovascular risk factor did not occur for that patient.

9.3 Treatments

Study treatment

The analysis of study treatment data will be based on the Safety set. The number of active and placebo injections received will be presented by treatment group and by epoch (study period) as appropriate.

The duration of exposure to study treatment will also be summarized by study treatment group. In addition, the number and percentage of patients with cumulative exposure levels (e.g. any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.) will be presented.

Prior and concomitant medications

Prior and concomitant medications will be summarized in separate tables by study treatment group. Prior medications are defined as treatments taken and stopped prior to the first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered.

For DMARDs, those DMARDs taken by patients since at least 3 months prior to Screening will be recorded.

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

9.4 Analysis of the primary variable

9.4.1 Variable

The primary analysis variable is the change from baseline in GLOESS over 12 weeks. The primary analysis of this study will evaluate:

- The superiority of secukinumab will be compared to placebo in PsA patients who have an IR to non-biologic DMARD with respect to the change from Baseline in GLOESS over 12 weeks.

The analysis of all efficacy variables will be based on the FAS.

9.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypothesis for the GLOESS being tested is that there is no difference in the mean change from baseline scores over 12 weeks in the secukinumab regimen vs the placebo regimen.

Between-treatment differences in the change in GLOESS will be evaluated using a mixed-effect model repeated measures model (MMRM) with treatment regimen, center, machine type and analysis visit as factors and weight and baseline GLOESS as continuous covariates. Treatment by analysis visit will be included as an interaction term in the model. An unstructured covariance structure will be assumed for this model. If the model does not converge, the compound symmetry covariance structure will be used. The data will be assumed to be missing at random (MAR).

9.4.3 Handling of missing values/censoring/discontinuations

Missing data for the ACR 20 response and other binary efficacy variables (e.g. ACR 50, ACR 70, MDA, PASI 75, PASI 90) for data up to 12 weeks (Week 12) will be handled as follows:

- Patients who drop out of the trial for any reason will be considered non-responders from the time they drop out through to Week 12.
- Patients who do not have the required data to compute ACR response (i.e. TJC and SJC and at least 3 of the 5 ACR core set variables) at the specific post-Baseline time points will be classified as clinical non-responders.

The following continuous variables: ACR components, HAQ-DI© score, PDUS score and its components will be analyzed using a MMRM, which is valid under the MAR assumption. For analyses of these parameters, if all post-baseline values are missing then these missing values will not be imputed and the patient will be removed from the analysis of the corresponding variable, i.e. it may be that the number of patients providing data to an analysis is smaller than the number of patients in the FAS.

Data collected during the open label period (after Week 12) will generally be presented as 'observed case'; i.e. all available data for each time point will be included in the analyses.

9.4.4 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.

For sensitivity analyses, an analysis will be performed with the observed data, and also with multiple imputations where patients without any post-baseline values are included. An additional sensitivity analysis will be conducted using a non-parametric analysis of covariance (ANCOVA) model (Koch et al 1998) with treatment regimen, baseline weight and PDUS score as exploratory variables.

9.5 Analysis of secondary variables

9.5.1 Key secondary efficacy variables

The key secondary efficacy variables are as follows:

- ACR 20 response at Week 12.
- ACR 50 response at Week 12.
- Change in SPARCC enthesitis index from Baseline to Week 12.

Testing strategy

The following hypotheses will be included in the testing strategy and type-I-errors will be set such that a family-wise type-I-error of 5% is kept:

Primary objective:

- H1: secukinumab s.c. is not different to placebo regimen with respect to the change in GLOESS from Baseline to Week 12.

See Section 9.4.2 for details.

Key secondary objectives:

- H2: secukinumab is not different to placebo regimen with respect to ACR 20 response at Week 12.
- H3: secukinumab s.c. is not different to placebo regimen with respect to ACR 50 response at Week 12.
- H4: secukinumab s.c. is not different to placebo regimen with respect to the change in SPARCC enthesitis index from Baseline to Week 12.

No hypotheses other than H_1 to H_4 will be considered. The family wise error will be set to α=5% (1-sided). The graphical approach of Bretz (Bretz et al 2009) for sequentially rejective testing procedures is used to illustrate the hierarchical testing strategy (Figure 9-1).

Figure 9-1 Testing strategy

The family-wise error will be set to α = 5% (1-sided). H1 is tested at α (1-sided). The following hypotheses will be tested sequentially and are included in the hierarchical testing strategy and type-I-errors will be set such that a family-wise type-I-error of 5% is kept:

The testing sequence will continue to H2 at α (1-sided) only if H1 has been rejected.

Similarly, the testing sequence will continue to H3 at α (1-sided) only if H2 has been rejected. This process will continue as each hypothesis is rejected up to H4.

Of note, in the description above, rejection of a hypothesis refers to rejection of the 1-sided hypothesis; however, the level of a rejected hypothesis is only passed on (according to the graphical procedure) for the test of another hypothesis if the treatment effect is in favor of secukinumab.

ACR 20 at Week 12

Response at Week 12 in ACR 20 in the FAS will be evaluated using a logistic regression model with study treatment as a factor and baseline weight as a covariate. The odds ratios will be computed for comparison of secukinumab versus placebo using the logistic regression model fitted. Firth's penalized maximum likelihood estimation method will be used in the event of non-convergence of the logistic regression model outlined.

ACR 50 at Week 12

Response at Week 12 in ACR 50 in the FAS will be evaluated using a logistic regression model with study treatment as a factor and baseline weight as a covariate. The odds ratios will be computed for comparison of secukinumab versus placebo using the logistic regression model fitted.

Changes in SPARCC at Week 12

Between-treatment differences in the change from baseline in SPARCC at Week 12 in the FAS will be compared by means of a MMRM with treatment regimen and analysis visit as factors and baseline weight and SPARCC score as continuous covariates. Study treatment by analysis visit will be included as an interaction term in the model. An unstructured covariance structure will be assumed for this model. The significance of the treatment effect for secukinumab at different analysis visits will be determined from the comparison to placebo.

9.5.2 Other secondary efficacy variables

The following secondary efficacy variables will be analyzed using the FAS population:

- Change in GLOESS from Baseline to Week 8.
- Change in OMERACT enthesitis score from Baseline to Week 8 for each of the 5 targeted entheses.

The between treatment differences will be compared by means of a MMRM with treatment regimen, center, machine type and analysis visit as factors and baseline weight and baseline score as continuous covariates. Study treatment by analysis visit will be included as an interaction term in the model. An unstructured covariance structure will be assumed for this model. The significance of the treatment effect for secukinumab at different analysis visits will be determined from the comparison to placebo. The OMERACT enthesitis score will be analyzed separately for each of the targeted entheses.

9.5.3 Exploratory efficacy variables

All the following exploratory efficacy variables will be analyzed on the FAS for all applicable analysis visits unless otherwise specified.

- Change from Week 12 in GLOESS of the ultrasound active joints out of 48 and its components to Week 24 and Week 52 for placebo group who switched to secukinumab at Week 12.
- Change from baseline in GLOESS of the ultrasound active joints out of 48 and its components to Week 24 and Week 52 for the secukinumab group.

- Change from Week 12 in OMERACT individual enthesitis scores to Week 24 and to Week 52 for placebo group who switched to secukinumab at Week 12.
- Change from baseline in OMERACT individual enthesitis scores to Week 24 and to Week 52 for secukinumab group.
- Correlation between single component of the SPARCC index and semi-quantitative Power Doppler in evaluate the improvement of each enthesitis site from baseline to Week 12.
- Correlation between patients achieving at least 20% improvement in GLOESS from baseline to Week 12.and patients achieving ACR 20 response of the same joints involved.
- Correlation between the PDUS response versus the SPARCC score at Week 12 in each enthesis.
- The response of ACR 20, ACR 50, ACR 70, PASI 75, PASI 90, dactylitis count, HAQ-DI© response at Week 24
- Change from Baseline in ACR components at Week 24:
  - Changes in TJC 78 over time.
  - Change in SJC 76 over time.
  - Change in patient's global assessment of disease activity.
  - Change in patient's assessment of PsA pain.
  - Change in Physician's global assessment of disease activity.
  - Change in HAQ-DI response over time.
  - Change in hsCRP.
- Proportion of patients achieving MDA at Week 24 and Week 52.
- Overall time spent on PDUS assessments of joint inflammation and enthesitis for the main study and breakdown of time spent on these assessments by visit.

All results from the exploratory efficacy analyses are to be interpreted descriptively.

Correlations between variables will be investigated through scatter plots; also Pearson's correlation coefficient will be presented when a linear relationship is assumed otherwise Spearman's rank correlation coefficient will be presented.

Variables whose distribution are not anticipated to be normal (i.e. hsCRP) will be transformed and analyzed on the $\log_e$ scale.

All other analysis of the exploratory variables will be outlined in the statistical analysis plan.

9.5.4 Substudy

[redacted]

[redacted]

9.5.5 Safety variables

Adverse events

Treatment-emergent AEs (i.e. events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose + 84 days) will be summarized.

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

These summaries may be presented separately by study periods.

The incidence of AEs will be presented per 100 patient years of exposure for the most frequent AEs (≥ 2% in any group), SAEs and selected SOCs to be outlined in the statistical analysis plan.

Separate summaries will be provided for death, SAEs, other significant AEs leading to discontinuation and AEs leading to dose adjustment (including study treatment discontinuation).

A graphical display of relative frequencies within each system organ class and relative risks, as appropriate, will be presented.

Laboratory data

The summary of laboratory evaluations will be presented for 3 groups of laboratory tests (hematology, serum chemistry and urinalysis). Descriptive summary statistics for the change from Baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and study treatment group. Change from Baseline will only be summarized for patients with both Baseline and post Baseline data. For each parameter, the maximum change from Baseline within each study period will be evaluated analogously.

In addition, shift tables will be provided for all parameters to compare a patient's Baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the Baseline value was normal, low, or high.

These summaries will be presented by laboratory test and study treatment group. Shifts will be presented by visit as well as for most extreme values post-Baseline.

Immunogenicity

Summary statistics will be provided for the percentage of patients with blood samples for immunogenicity (anti-AIN457 antibodies). If appropriate, shift tables will also be presented.

Vital signs

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

Physical examination

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

Pregnancy tests

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

9.5.6 Resource utilization

Not applicable.

9.5.7 Pharmacokinetics

All patients with concentration data will be included in the pharmacokinetic data analysis.

Pharmacokinetic variables

The following pharmacokinetic parameter will be determined: Cmin,ss. Cmin,ss will be determined using Phoenix software. Individual serum concentrations in µg/ml will be listed. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the limit of quantification will be treated as zero in summary statistics for concentration data only. During modeling of the pharmacokinetics of secukinumab, the broad principles outlined in the FDA Guidance for Industry: Population Pharmacokinetics will be followed.

Statistical methods for pharmacokinetic analyses

Summary statistics by visit/time will be provided for the above mentioned parameter and will include arithmetic and geometric means, SD, median, minimum and maximum. Individual concentrations will be listed by patient.

9.5.8 Pharmacogenetics/pharmacogenomics

Not applicable.

9.5.9 Biomarkers

Not applicable.

9.5.10 PK/PD

Not applicable.

9.6 Interim analyses

Prior to the final database lock and end of study reporting there will be 3 interim analyses:

- Blinded sample size re-estimation (SSR)
- Week 12 interim analysis
- Week 24 interim analysis.

After these 3 interim analyses, there will be one final study database lock i.e. once the last patient has completed the Week 64 /EOS visit or early withdrawal visit (in case the last patient withdraws early from the study).

Blinded Sample Size Re-estimation (SSR)

The blinded SSR will be performed when the first 60 patients have completed the Week 12 visit. The pooled standard deviation of the change from baseline in GLOESS at Week 12 will be calculated for the 60 patients and the pooled change will be transformed based on the placebo response observed in the FUTURE 2 study (CAIN457F2312), roughly 50% of secukinumab. These estimates will be used to decide whether the study should continue as planned. Although the study is originally designed to have at least 90% power, any change in sample size will be based on 80% power due to enrolment feasibility.

Week 12 analysis

The analysis of the primary and secondary efficacy variables will be performed after all patients complete the Week 12 visit. This analysis will also include exploratory variables outlined up to Week 12 and all available safety data.

Week 24 analysis

The analysis of the exploratory variables up to Week 24 will be performed after all patients complete the Week 24 visit. This analysis will also include all available safety data.

9.7 Sample size calculation

This study was designed using data for abatacept in the APPRAISE study (RA study to assess early response to abatacept + MTX (D'Agostino et al, 2016), to test the superiority of secukinumab compared to placebo at the 5% significance level using a 2-sided test. Assuming a difference in the mean change from Baseline at Week 12 in OMERACT global PDUS score of -5.8 with a pooled standard deviation of 13.2, 218 patients in total (109 patients per arm) were estimated to achieve a power of 90% (EAST 6).

A blinded SSR was performed once the first 60 patients completed the Week 12 visit to evaluate the assumptions used in the sample size calculations. The statistical test for the primary endpoint has been changed from a 2-sided to a 1-sided test.

The first 60 patients to reach Week 12 have a pooled mean change from Baseline at Week 12 in OMERACT global PDUS score of -5.25 with a pooled standard deviation of 9.527. Using the estimated placebo effect of roughly 50% of secukinumab based on data from the FUTURE 2 study (CAIN457F2312) as in the original sample size calculation, the pooled PDUS score change of -5.25 translates to an assumed change of -7.000 and -3.500 for the secukinumab and placebo group, respectively, providing a difference of 3.500 between the groups. Adapting the original sample size calculation to be 1-sided with the power relaxed to 80%, 184 patients in total (92 patients per arm) are required (EAST 6).

At the time of the blinded sample size calculation, 72 patients were available who had reached their Week 12 visit, to provide the most accurate estimation, all data available were considered i.e. the first 72 patients as opposed to the first 60 patients. Using all available data a difference in the mean change from Baseline at Week 12 in OMERACT global PDUS score of 4.352 was observed with a pooled standard deviation of 9.822. At the 5% significance level using a 1sided test, 126 patients are needed to achieve a power of 80% (EAST 6).

The 2 calculations produce a sample size range of 127-185 patients; thus, the sample size will be adjusted to a new target of 164 patients in total (82 patients per arm). This is mid-way point of the range plus a 5% adjustment based on the observed drop-out rate of patients prior to Week 12 observed at the time of this calculation.

For the secondary variables:

Patients who were naive to TNFα inhibitors where pooled from the 2 confirmatory studies in PsA for secukinumab (CAIN457F2306 and CAIN457F2312) and a placebo response rate of about 29.6% and 10.7% at Week 12 was observed for ACR 20 and ACR 50 respectively. From the same studies pooled, the response rate to secukinumab 150 mg s.c. was around 63.5% (ACR 20) and 33.3% (ACR 50), and the response rate to secukinumab 300 mg s.c. was around 67.2% (ACR 20) and 37.3% (ACR 50). Taking a conservative approach due to the pooled groups, the lowest response rate between the secukinumab arms (i.e. ACR 20 = 63.5% and ACR 50 = 33.3%) was used to estimate the secukinumab response, which resulted in the study having greater than 90% power to detect a difference to placebo using the current sample size.

It is not possible to calculate the power for the SPARCC or early therapeutic effect on affected enthesitis variables due to lack of data available.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP with applicable local regulations including the European Directive 2001/20/EC, the Medical Research Involving Human Subjects Act in the Netherlands (known as the WMO in Dutch), the US Code of Federal Regulations 21, and with the ethical principles laid down in the World Medical Association (WMA) Declaration of Helsinki (DOH) 1964 and amendments thereof, most recently 2013 (WMA DOH 2013).

10.2 Informed consent procedures

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

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

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

Two additional informed consent forms will be provided for patient sign-off in this study; one to confirm the patient would like to enter into the extension period of the study (see Section 3.1); and one to confirm the patient would like to participate in an optional sub-study [redacted] The sub-study will only apply to patients attending study centers [redacted].

It is required as part of this protocol that the Investigator presents the option to participate in the extension period to all patients; and presents the option to participate in the sub-study to all applicable patients (i.e. patients attending study centers involved in the sub-study).

The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in the extension period of the study, or to participate in the sub-study (for applicable patients as described above), will in no way affect the patient's ability to participate in the main research study.

The will be performed at study centers [redacted].

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the Investigator/institution should obtain approval/favorable opinion from the IRB/IEC for the study protocol, written informed consent form, 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.

10.4 Publication of study protocol and results

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

11 Protocol adherence

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

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

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the Investigator is

expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 (Safety Monitoring) should be followed.

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13 Appendices

13.1 Appendix 1: 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 at the same time as sent to the Investigators. Any intervention based on these laboratory values should be discussed with Novartis personnel.

Table 13-1 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

13.2 Appendix 2: Liver event and laboratory trigger definitions

Table 13-2 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*

Abbreviations: ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, INR: international normalized ratio, ULN: upper limit of normal

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

Table 13-3 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 CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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 CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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 CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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 CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at Investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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 CRF	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	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at Investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin,

Criteria	Actions required	Follow-up monitoring
	• Complete liver CRF	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 CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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 CRF	Investigator discretion

Abbreviations: Alb: Albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRF: case report form, GGT: gamma glutamyl transferase, INR: international normalized ratio, LFT: liver function test, PT: prothrombin test, TBL: total bilirubin, ULN: upper limit of normal.

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

[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 3 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.

13.3 Appendix 3: The classification criteria for psoriatic arthritis (CASPAR)

To meet the classification criteria for psoriatic arthritis (CASPAR) for diagnosis of psoriatic arthritis according to (Taylor 2006) a patient must have inflammatory articular disease (joint, spine or entheseal) and at least 3 points from the following 5 categories:

1. 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**).
2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination (**1 point**).
3. A negative test result for the presence of rheumatoid factor by any method except latex (**1 point**).
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist (**1 point**).
5. 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 patient. If the total score is ≥ 3, the patient meets the CASPAR criteria for psoriatic arthritis diagnosis.)

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

13.4 Appendix 4: American College of Rheumatology measures and criteria of response

Number of tender joints:

Joint counts 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 78 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 2 first carpometacarpal, 10 MCP, 10 PIP, 8 distal interphalangeal joints of the hands, the 2 hip, 2 knee, 2 talo-tibial, 2 mid-tarsal, 10 MTP, 10 PIP, and 8 DIP joints of the feet.

Joint tenderness and swelling are to be graded present (1) or absent (0).

Number of swollen joints:

Joints are to be scored as either swollen (1) or not swollen (0). The 76 joints to be examined for swelling are the same as those examined for tenderness, however excluding both hip joints.

Patient's assessment of psoriatic arthritis 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."

Physician's global assessment of disease activity

On a 100 mm non-anchored visual analog scale, from no arthritis activity to maximal arthritis activity.

Patient's assessment of physical function

Health Assessment Questionnaire – HAQ-DI©

ACR 20/50/70*

A patient will be considered as improved according the ACR 20 criteria* if she/he has at least 20% improvement in the 2 following measures:

- Tender joint count.
- Swollen joint count.
- and at least 3 of the following 5 measures:
  - Patient's assessment of pain
  - Patient's global assessment of disease activity
  - Physician's global assessment of disease activity
  - Health assessment questionnaire (HAQ©) score
  - C-reactive protein (CRP) or erythrocyte sedimentation rate (note: CRP only will be assessed in this study)

ACR 50 = 50% improvement in at least 3 of the 5 measures and 50% improvement in the swollen and tender joint count.

ACR 70 = 70% improvement in at least 3 of the 5 measures and 70% improvement in the swollen and tender joint count.

Reference:

Felson DT, Anderson JJ, Boers M, et al (1995) American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum; 38(6):727-35.

13.5 Appendix 5: Joint assessments

Joint counts will be performed by a clinical assessor with experience in performing examinations in clinical trials. Every effort must be made to ensure that the same clinical assessor completes the swollen and tender joint counts for each patient. Visits requiring joint assessment should be scheduled according to the availability of the evaluator. If the same clinical assessor is unable to complete the joint assessments, then a qualified individual, with overlapping experience may perform the evaluation.

Assessments of clinical efficacy must be performed by the same assessor(s) throughout the study. The clinical assessor(s) must be a different person from the one performing the ultrasound (US) assessments. Personnel cannot be involved in assessing clinical efficacy in one visit and serve as an ultrasound assessor in another visit. Clinical joint assessments should be performed at approximately the same time of day during the study. Patients should be reminded to avoid taking their weekly dose of MTX during the 48 hours prior to these visits.

13.6 Appendix 6 OMERACT-EULAR Global PDUS OMERACT out of 48 joints

The Outcome Measures in Rheumatology-Ultrasound (OMERACT-US) Task Force, with funding received from the European League Against Rheumatism (EULAR), works to standardize the use of ultrasonography in rheumatoid arthritis (RA) and has developed a composite scoring system (the OMERACT-EULAR composite PDUS score) to detect and score synovitis. This score combines Greyscale-assessed synovial hyperplasia with an intra-synovial power Doppler signal for evaluating synovial activity. The score has demonstrated validity and intra- and inter-observer reliability in cross-sectional datasets, applicability to all joints and consistency between machines

Medium- to high-level ultrasound machines will be used (Esaote Technos MPX MyLab 70, GE Logic [Series 9] or Siemens Acuson Antares), employing high-frequency (12-18 MHz) transducers. Doppler parameters will be adjusted according to the device used (range of pulse repetition frequency 400–800 Hz; Doppler frequency 7–14.1 MHz). Power Doppler ultrasound evaluation will be performed at each site by an independent expert in musculoskeletal ultrasound who will be kept blinded from clinical evaluations.

The PDUS assessment will consist of an evaluation of hypoechoic synovial hyperplasia (SH) and joint effusion (JE) using Greyscale and of synovial vascularization using Power Doppler. The pre-specified set of 24 paired joints will be scanned at each visit on the dorsal aspect, with the joint in a neutral position, except for the knee, which will also be examined in a flexed position (30°). Standardized joint and probe positions will be used, based on a reference atlas, which also shows examples of synovitis grading for each site examined.

The presence of synovitis (i.e. SH and Power Doppler, without JE) will be scored according to the OMERACT-EULAR PDUS composite semi-quantitative scale (0 to 3; Table 13-4). Each single component of joint inflammation (SH, Power Doppler, JE) was also scored separately at each visit, using semi-quantitative scales (0 to 3; Table 13-4). The global PDUS scores for the 24 paired joints will then be calculated using the sum of the composite PDUS scores for all joints examined, giving a potential score and of 0 to 144 for the 24 paired joints.

In an attempt to ensure homogeneity of synovitis scoring across sites, all PDUS assessors will be required to complete a training session and examinations at each center in order to be

qualified for PDUS evaluation in this study. Quality control assessment of the scoring will be performed for the first patient included from each center and once all patients have completed the study (i.e. following the last patient's last visit) when the last patient enrolled in the trial has completed their last visit.

Table 13-4 Ultrasound scoring system

Greyscale ultrasound	
Joint effusion	
Grade 0	No effusion
Grade 1	Minimal amount of joint effusion
Grade 2	Moderate amount of joint effusion (little distension of the joint capsule)
Grade 3	Extensive amount of joint effusion (with high distension of the joint capsule)
Inflammatory or active synovial hyperplasia (hypoechoic)	
Grade 0	No hypoechoic synovial thickening
Grade 1	Minimal hypoechoic synovial thickening (filling the angle between the periarticular bones, without bulging over the line linking tops of the bones)
Grade 2	Hypoechoic synovial thickening bulging over the line linking tops of the periarticular bones but without extension along the bone diaphysis
Grade 3	Hypoechoic synovial thickening bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphysis
Power Doppler signal	
Grade 0	No flow in the synovium
Grade 1	Up to 3 single spots signals or up to 2 confluent spots or 1 confluent spot plus up to 2 single spots
Grade 2	Vessel signals in less than half of the area of the synovium (< 50%)
Grade 3	Vessel signals in more than half of the area of the synovium (> 50%)
OMERACT-EULAR composite PDUS score (for individual joints)	
Grade 0 (normal joint)	No greyscale-detected synovial hyperplasia or Power Doppler signal
Grade 1 (minimal synovitis)	Minimal synovial hyperplasia and ≤ Grade 1 Power Doppler signal
Grade 2 (moderate synovitis)	Moderate synovial hyperplasia and ≤ Grade 2 Power Doppler signal or minimal synovial hyperplasia and a Grade 2 Power Doppler signal
Grade 3 (severe synovitis)	Severe synovial hyperplasia and ≤ Grade 3 Power Doppler signal or moderate synovial hyperplasia and a Grade 3 Power Doppler signal
Global OMERACT-EULAR synovitis score (GLOESS)	Sum of composite PDUS scores for all joints assessed (e.g. for MCPs 2–5, Global PDUS score would range from 0 to 24)

13.7 Appendix 7: OMERACT score of enthesitis

Evaluation of entheses

For the evaluation of enthesitis, ultrasound will initially be performed in B mode to detect morphologic abnormalities and subsequently with power Doppler to detect abnormal vascularization at bony insertions.

This score was developed following an initial Delphi exercise undertaken to define enthesitis and its core components. These definitions were subsequently tested on static images taken from SpA patients in order to evaluate their reliability (Tersley et al 2014). Excellent agreement was obtained for separating signs of active inflammation from signs of structural damage. A definition was therefore proposed that included hypoechogenicity, thickening, and Doppler signal as signs of inflammation (and therefore of acute/active US enthesitis) and included erosions, enthesophytes, calcification, and cortical irregularities as signs of structural damage (and therefore of chronic/ inactive US enthesitis). These are as follows:

- Hypoechogenicity was defined as a lack of the homogeneous fibrillar pattern with loss of the tightly packed echogenic lines after correcting for anisotropy.
- Increased thickness of the enthesis was defined as increased thickness of the tendon/ligament/capsule insertion into the bone, as compared to the body of the tendon/ligament/ capsule, with or without blurring of the tendon/ligament/ capsule margins.
- Enthesophytes were defined as a step up of bony prominence at the end of the normal bone contour, seen in 2 perpendicular planes, with or without acoustic shadow.
- Calcifications were defined as hyperechoic (bright) foci consistent with calcific deposits, with or without acoustic shadow, seen in 2 perpendicular planes, detected at the tendon insertion into the bone (i.e. enthesis).
- Erosion was defined as a cortical breakage with a step down contour defect, seen in 2 perpendicular planes, at the insertion of the enthesis to the bone, according to the OMERACT definition.
- The Doppler signal at the enthesis was defined as Doppler activity approximately 2 mm near the bony cortex. The Doppler signal must be at the enthesis, different from reflecting surface artifact or nutrition vessel signal, with or without cortical irregularities, erosions, or enthesophytes.

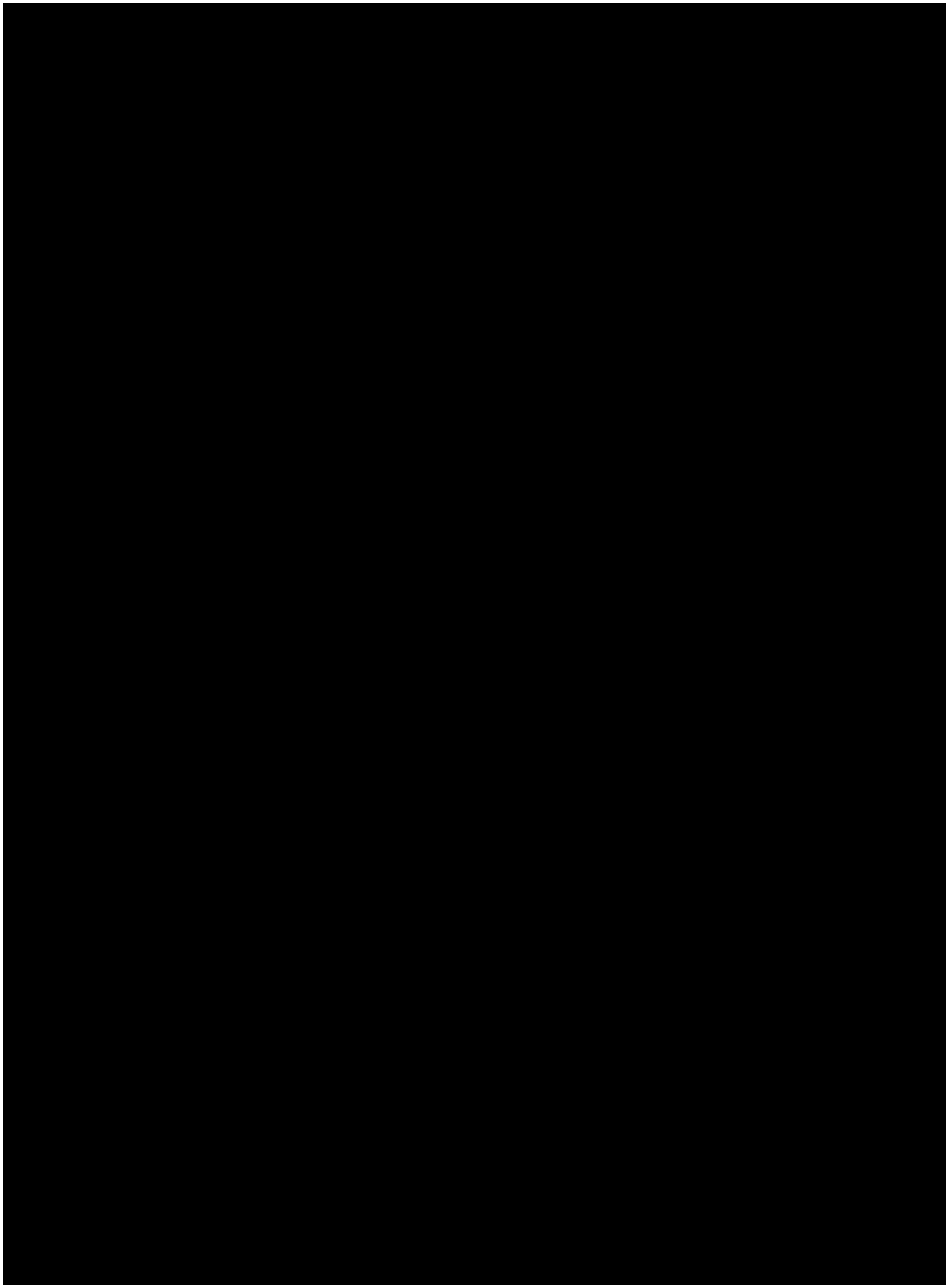
The following entheses will be examined bilaterally:

1. Common extensor tendon at its insertion at the lateral humeral epicondyle.
2. Quadriceps tendon at its insertion at the superior pole of the patella.
3. Patellar tendon at its proximal insertion at the inferior pole of the patella.
4. Patellar tendon at its distal insertion at the tibia tuberosity.
5. Calcaneal insertions:
   a. Achilles tendon at its insertion at the calcaneus.
   b. Plantar aponeuroses at its insertion at the calcaneus.

Each affected enthesis out of 5 targeted entheses will be scored on inflammatory and morphological components according to the OMERACT enthesitis composite semi-quantitative scale (0 to 3) as shown in Table 13-5.

Table 13-5 Severity grade of enthesitis

Severity scoring	Morphological (B mode)	Inflammation (Doppler)
0	No abnormalities	0 Doppler signal
1	Hypoechogenicity alone	1 or 2 Doppler Spots at cortical insertion
2	Thickening and hypoechogenicity plus calcifications/enthesophytes	More than 2 Doppler spots at cortical insertion and up to 2 mm from cortical bone
3	Thickening and hypoechogenicity plus calcifications/enthesophytes AND erosions	Extensive Doppler signal at cortical insertion



[redacted]

13.9 Appendix 9: PDUS equipment

When performing a sonographic examination, it is important to use a high frequency sonographic probe that allows use of the Doppler mode. These high frequency probes have excellent resolution and are designed specifically for the exploration of muscular and articular superficial structures.

The following equipment is required for CAIN457F2354: high quality equipment with both a high quality Gray-scale setting (linear array transducer with a frequency between 12 MHz and16 MHz) and a high quality Doppler device. The presence of a power Doppler system is preferred to a color Doppler or an energy Doppler system only. Power Doppler parameters will be chosen according to the best setting of each machine, with a pulse repetition frequency (PRF) around 500-800 Hz.

The US equipment of each center will be chosen among a list of equipment featuring both a high quality Gray-scale setting and a high quality power Doppler device. This will ensure appropriate image quality for the evaluation of progression of psoriatic arthritis. The following equipment configurations are appropriate for CAIN457F2354 (Table 13-9):

Table 13-9 PDUS equipment recommendations

Manufacturer	Model	Doppler		Diccom	HF Probe (> 12 MHz)
		Power Doppler	Color/ Energy Doppler		
ESAOTE	Technos MPX Mylab 70	Yes	Yes	Yes	Yes
Acuson	Antares	Yes	Yes	Yes	Yes
GE	Logic Series 9	Yes	Yes	Yes	Yes
Siemens		Yes	Yes	Yes	Yes

13.10 Appendix 10: Health assessment questionnaire

The Health Assessment Questionnaire (HAQ©, Fries JF et al 1980) is a validated measure of physical disability and functional status. It has 4 dimensions: disability, pain, drug side effects and dollar costs, although, the latter 3 are rarely used in clinical trials. In this trial only the disability dimension will be used. The disability dimension consists of 20 multiple choice items concerning difficulty in performing eight common activities of daily living; dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping and activities. Patients choose from 4 response categories, ranging from “without any difficulty” to “unable to do”. The ACR Rheumatology Committee on Outcome Measures in RA recommends the use of this questionnaire in clinical trials.

Scoring of the HAQ©

The HAQ© will be scored in accordance with the recommendation from the developers outlined in the "HAQ PACK" from Stanford University, California. The following coding is to be used for the 8 categories of the disability outcome dimension:

Without ANY difficulty	0
With SOME difficulty	1
With MUCH difficulty	2
UNABLE to do	3

Within each of the 8 categories only the item indicating the most severe impairment contributes to the category score. If the patient requires the use of aids, devices, or help from another to accomplish any of the activities in an associated category, then the score for that category will be assigned the value 2, unless the score is already 3 (i.e. scores of 0 or 1 are increased to 2). Associated categories are defined in the "HAQ PACK".

From the scores for each category a standard disability index (SDI) is computed by summing the computed scores for each category and dividing by the number of categories answered. The SDI is not computed if the patient does not have scores for at least 6 categories. This SDI is the HAQ© score, which will be used in the statistical analyses of this instrument. The range for this score is (0, 3).

HAQ© Data Collection

The HAQ© is 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 on the electronic device and ensure that the center number, patient's number and initials are identical to the Case Record Form. As there are no source data for this questionnaire, the data queries will be restricted to patient/visit information.

13.11 Appendix 11: Standard reference table for the LDI

Table-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-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