Clinical Development

Secukinumab (AIN457)

AIN457F2354

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

Statistical Analysis Plan (SAP)

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29-Mar-2021/ Amendment 5		Section 2.1 - Data analysis general information Section 2.2.1 – Subgroup of interest Section 2.9.1.1 – Adverse events of special interest / grouping of AEs [redacted]
18-Feb-2021 / Amendment 4	Refinement of analysis requirements prior to DBLK	Section 2.1 - Data analysis general information Section 2.2.1 – Subgroup of interest Section 2.3.2 – Demographics and other baseline characteristics Section 2.4.1 – Study treatment / compliance Section 2.5.4 – Supportive analyses Section 2.6.2 – Statistical hypothesis, model, and method of analysis Section 2.6.3 – Handling of missing values/discontinuations Section 2.6.4 – Supportive analysis Section 2.8 – Other efficacy variables / exploratory analysis [redacted] Section 2.9.1 – Adverse events Section 2.14 - Sub study Section 4 – Change to protocol specified analyses

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		Section 5.4 – Assessment windows Section 5.10 - OMERACT-EULAR Global PDUS OMERACT out of 48 joints [redacted] Section 6 - References
09-SEP-2020 / Amendment 3	Additional efficiency measures and treatment label for Adverse event summaries clarification	Section 2.1 – Data analysis general information Section 2.2.1 - Subgroup of interest Section 2.3.2 – Demographics and other baseline characteristics Section 2.4.2 – Prior & Concomitant medications Section 2.8 – Other efficacy variables / exploratory analysis Section 2.9 – Safety analyses Section 2.9.1 – Adverse events Section 2.9.1.1 – Adverse events of special interest / grouping of AEs [redacted] Section 5.13 – Health assessment questionnaire [redacted]
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	derivations for OMERACT (PDUS) enthesitis scores	Section 5.10 - OMERACT-EULAR Global PDUS OMERACT out of 48 joints Section 5.11 - OMERACT score of enthesitis
04-Mar-2020 / v2 (Amendment 1)	To incorporate updates made in Protocol Amendments 2 and 3 & during Dry run review	Section 1 – Introduction Section 1.1 – Study design Section 1.2.3.1 – Sub-study objectives Section 2.1 – Data analysis general information Section 2.2.1 – Subgroup of interest Section 2.3.2 – Demographics and other baseline charcateristics Section 2.4.1 – Study treatment/compliance Section 2.4.2 – Prior & Concomitant medications Section 2.5.4 – Supportive analysis Section 2.6.1 – Key secondary endpoint Section 2.6.3 – Handling of missing values/discontinuations Section 2.6.4 – Supportive analysis Section 2.7.1 – Secondary endpoint Section 2.7.2 – Statistical hypothesis, model & method of analysis Section 2.7.3 – Handling of missing values/discontinuations Section 2.8 – Other efficacy variables / exploratory analysis [redacted] Section 2.9.1 – Adverse events

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		Section 2.9.1.1 – Adverse events of special interest / grouping of AEs Section 2.9.5 – Laboratory data Section 2.9.7.2 – Vital signs Section 2.10 – Pharmacokinetic endpoints Section 2.15 – Interim analysis Section 3.1 – Determination of sample size Section 4 – Change to protocol specified analyses Section 5.2 – AEs coding/grading Section 5.4 – Assessment windows Section 5.5.1 – Primary analysis Section 5.5.2 – Key scondary analysis Section 5.6 - Rule of exclusion criteria of analysis sets Section 5.14 - PASI

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ANA	Antinuclear antibodies
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
BSA	Body Surface Area
CASPAR	Classification Criteria for Psoriatic Arthritis
CHMP	Committee for Medicinal Products for Human Use
[redacted]	[redacted]
DBLK	Database Lock
DMARD	Disease Modifying Anti-Rheumatic Drug
FAS	Full Analysis Set
ECG	Electrocardiography
eCRF	Electronic Case Report Form
EULAR	European League Against Rheumatism
GLOESS	Global OMERACT-EULAR Synovitis Score
HAQ-DI	Health Assessment Questionnaire – disability index
IR	Inadequate response
JE	Joint Effusion
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
MAR	Missing at Random
MCAR	Missing Completely at Random
MCMC	Markov Chain Mone Carlo
MCP	Metacarpophalangeal
[redacted]	[redacted]
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed Model Repeated Measures
MTP	Metatarsophalangeal
MTX	Methotrexate
OMERACT	Outcome Measures in Rheumatology
PASI	Psoriasis area and severity index
PD	Protocol Deviation
PDUS	Power dopper Ultrasound Sonography
PFS	Prefilled syringes
PK	Pharmacokinetics
PID	Distal interphalangeal
PIP	Proximal interphalangeal
PPD	Purified Protein Derivative
PsA	Psoriatic Arthritis
[redacted]	[redacted]

RF	Rheumatoid Factor
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SDI	Standard Disability Index
SH	Synovial Hyperplasia
SOC	System Organ Class
SpA	Spondyloarthritis
SJC	Swollen Joint Count
SPARCC	Spondyloarthritis Research Consortium of Canada
SRM	Standarized Response Mean
SSR	Sample Size Reestimation
TEAE	Treatment Emergent Adverse Events
TJC	Tender Joint Count
VAS	Visual Analogue Scale
[redacted]	[redacted]

1 Introduction

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 psoriatic arthritis (PsA) despite non-biologic DMARDs. This study is designed to leverage the sensitivity of Power Doppler 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 to non-biologic DMARDs.

[redacted]

This document is based on the Clinical Study Protocol CAIN457A2354 v3 dated 27th November 2018. A Clinical Study Report will be prepared following the analysis outlined in this SAP.

1.1 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), a 12-week open-label treatment period (Period 2) and a 6-month open-label extension period (Period 3), and a 12-week follow-up period after treatment completion.

Screening period

Eligible patients will be enrolled and enter a 1 to 4- week Screening period prior to randomization.

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)
- **Group 2**: placebo

At each study treatment 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.

Primary analysis

The Week 12 analysis will be performed after all patients complete the Week 12 visit (see Section 2.15). Only the data analysts will be unblinded to the Treatment Period 1 randomization data after the Week 12 database lock/analyses. Summary results will be shared internally and externally; however, individual unblinded patient data will not be disclosed externally. The Ultrasonography Investigator and the Clinical Investigator will remain blinded from each other until the final database lock.

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

From **Week 12**, secukinumab will be given open-label to all patients irrespective of their initial treatment (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 until Week 24 (i.e. at Week 12, 16 and 20), based on their clinical characteristics (BSA or severity of skin lesions) at Week 12.

A blinded sample size estimation (SSR) will be performed when the first 60 patients have completed the Week 12 visit as described in Section 2.15.

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.

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 at either the study site (i.e. Week 24, 36 and 52) or at home (Week 28, 32, 40, 44, 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) will be withdrawn from the study.

The Week 24 analysis will be performed after all patients complete the Week 24 visit (see Section 2.15).

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.

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.

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 active disease as assessed by ≥ 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 and at least one clinical enthesitis at Screening and Baseline. 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.

1.2 Study objectives and endpoints

1.2.1 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 inadequate response (IR) to non-biologic DMARDs.

1.2.2 Secondary objectives

1.2.2.1 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.

1.2.2.2 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.

1.2.3 Exploratory objectives

[redacted]

- 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, PASI 100, [redacted]

1.2.3.1 Sub-study objectives

[redacted]

2 Statistical methods

2.1 Data analysis general information

The analysis outlined in this document will be performed by Novartis using SAS version 9.3 or higher software. All analyses outlined will also be performed by Novartis.

Comparative efficacy analyses (i.e. inferential efficacy comparisons with placebo) will focus on the time period when both active drug and the placebo are given in a manner suitable for making comparisons (e.g. double-blind). For AIN457F2354 this is the first 12-weeks of treatment. Comparative efficacy will be performed based on the FAS population using the randomized treatment. After week 12, the active secukinumab regimens will be compared using confidence intervals on the FAS population using treatment sequence. These treatment sequences represent the treatment combinations the subjects experience over the course of the entire trial in case of treatment switch at week 12.

The Week 3 efficacy assessment was removed from the study assessments in Protocol Amendment 2. Statistical comparisons at week 3 will not be presented due to the low number of subjects enrolled prior to this amendment.

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

The statistical analysis planned for the primary and secondary objectives are clearly stated, if not otherwise specified 95% confidence intervals may be presented along with point estimates and p-values will be presented as 1-sided.

Data analyses and summaries will be performed by treatment group (Secukinumab 150mg + 300 mg and Placebo) for baseline measurements, efficacy and safety data captured within the placebo-controlled period and for adverse events throughout the treatment periods.

Analyses of all efficacy and non-AE safety parameters for the treatment periods will be performed by treatment sequence and results presented for the following groups: secukinumab (150 mg + 300 mg), placebo – secukinumab (150 mg + 300 mg).

All listings will be presented by treatment sequence for efficacy and non-AE safety and by treatment for baseline and AE listings.

2.1.1 General definitions

Treatment periods

Period 1 = from first dose up to but not including Week 12 dose.

Period 2 = Week 12 dose up to but not including Week 24 dose.

Extension = Week 24 dose until Week 52.

Follow-up = After Week 52 until Week 64

Study Day 1 and other study days

The first day of administration of randomized study treatment (first dose) is defined as *Study Day 1* or *Day 1*.

All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day for a particular event date is calculated as [Date of event] – [Date of first dose]+1, i.e., Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively. For the dates before Day 1, study day for an event date is calculated as [Date of event] – [Date of first dose], i.e., Day -1, Day -2, etc., will be one day, two days, etc., before Day 1, respectively. Duration of an event will be calculated as (Event end date – Event start date + 1).

The descriptor “Day 0” will not be used.

Screening, baseline and post-baseline definitions

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the date of first dose of study treatment. Per protocol, subject informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of screening period. Any assessment

obtained during the screening period will be labeled screening assessment. Assessments made on Day 1 may occur before or after the randomization or the first dose.

For efficacy analyses, baseline is the last assessment (including unscheduled visits) obtained before the first dose of study treatment . All assessments obtained after the first dose of study treatment are considered as post-baseline unless otherwise specified.

For safety analyses, baseline is the last assessment (including unscheduled visits) obtained before the first dose of study treatment. All assessments obtained after the first dose of study treatment are considered as post-baseline unless otherwise specified.

Of note, re-randomization will not be used for baseline definition and only one baseline value will be defined referring to the first randomization.

Day of last dose of randomized study treatment

The date of last dose will be collected via the eCRF. The subject's exposure will be calculated considering the end of treatment period visit (e.g., treatment period 3 completion visit). If a subject discontinued early, then the last visit during the treatment period is considered (e.g. last visit in treatment period 2, if subject discontinued from treatment period 2).

2.2 Analysis sets

The following analysis sets will be used for the data analysis.

All screened patients : The all screened patients set will comprise all patients screened regardless of whether they were enrolled. Screen failures will be included.

Randomized set (RAN): 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 (SS): 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.

[redacted]

[redacted]

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of subjects screened will be presented. In addition, the reasons for screen failures will be provided. The number and percentage of subjects in the randomized set (who completed study periods) and who discontinued the study prematurely (including the reason for discontinuation) will be presented by study period for each treatment group and all subjects.

For each protocol deviation, the number and percentage of subjects for whom the deviation applies will be tabulated.

2.3.2 Demographics and other baseline characteristics

The following common background and demographic variables will be presented for the randomized set.

Continuous variables:

- Age (which is derived from date of birth and the screening assessment date)
- Height
- Weight
- Body mass index (BMI)

Body Mass Index (*BMI*) will be calculated using the following formula:

$$\text{BMI} = (\text{body weight in kilograms}) / (\text{height in meters})^2$$

For BMI, height and body weight used is the last value prior to first dose. If there is no weight recorded prior to taking of study treatment, BMI will be missing.

Categorical variables:

- Age categories (<65 years, 65 years and older, 75 years and older)
- Sex
- Race
- Ethnicity
- Source of patient referral
- Child bearing status
- Smoking status at baseline

Additionally the following psoriasis specific baseline characteristics and history of disease will be summarized:

- Baseline total BSA (≤3%, >3%)
- Baseline PASI
- Severity of psoriasis (CHMP guidelines, mild (total BSA <10% or PASI < 10), moderate ((PASI ≥10 or total BSA≥10%) and PASI ≤20 and total BSA ≤20%), severe (total BSA >20% or PASI > 20))
- Moderate-to-severe Psoriasis (EMA criteria : total BSA >10% or PASI > 10, FDA criteria : total BSA ≥10% and PASI ≥ 12
- CASPAR
- Global PDUS (GLOESS)
- SPARCC enthesitis index
- ACR components
- Time since diagnosis of psoriatic arthritis
- Time since diagnosis of psoriasis
- Previous exposure psoriasis therapies if applicable /PsA therapies
- QuantiFERON TV-Gold test or PPD skin test (depending on local guidelines)

- [redacted]
  - Distribution of patients by enthesitis severity at baseline; clinical enthesitis, Global and Total OMERACT enthesitis score at site level, number of enthesis involved per patient, and proportion of patients presenting with ultrasound OMERACT enthesitis >0 and its core components B Mode >0 and PD signal > 0
- [redacted]
  - Proportion of PDUS (GS+ PD) synovitis by joint

Unless otherwise specified, summary statistics will be presented for continuous variables for all subjects in the FAS. Similarly the number and percentage of subjects in each category will be presented by treatment group for categorical variables for all subjects in the FAS.

2.3.3 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 will be presented for the randomized set. 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 will be presented for the randomized set. 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.

2.4 Treatments (study treatment, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

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

The number of active and placebo injections will be summarized by treatment group and treatment period.

In case it cannot be identified from the data collected or assumed from the planned treatment whether an injection contained placebo or secukinumab, as if this occurs for subjects in the 300 mg treatment groups or in the placebo treatment group, respectively,

when subjects should receive two identical injections, it will be assumed that they received secukinumab or placebo, respectively, as planned.

The duration of exposure to study treatment will be summarized by the actual treatment received or treatment sequence for each treatment period. In addition, the number of subjects with cumulative exposure of at least certain time thresholds will be displayed. The following categories will be presented: "any exposure", "<1 week", "≥1 week" "≥2 weeks", "≥3 weeks", "≥4 weeks", "≥8 weeks", "≥12 weeks", and so on with an increase of time threshold by 4 weeks until there are no subjects in the category or the last category is presented.

For treatment period 1, the end date for the calculation of duration of exposure will be the earlier of:

a. Date of last injection in treatment period 1 + 84 days, and
b. Date of first injection in treatment period 2

For treatment period 2, the end date for the calculation of duration of exposure will be the earlier of:

a. Date of last injection in treatment period 2 + 84 days, and
b. Date of first injection in treatment period 3

For treatment period 3 (extension period), the end date for the calculation of duration of exposure will be the date of last injection in treatment period 3 + 84 days.

For patients with death as an event, end date for calculation of duration of exposure will be the date of death if it is earlier than the date of last injection + 84 days.

Duration of exposure (years) = duration of exposure (days) / 365.25

The analyses of duration of exposure described above will be done for the double-blind placebo controlled period (Period 1), Treatment Period 2 – open-label treatment period (Week 12 to Week 24) and Treatment Period 3 – extension period (Week 24 to Week 52).

Compliance

Compliance will be calculated based on documented study drug administrations and displayed by treatment group. It is calculated as follows:

Compliance (%) = 100*(total no. of injections administered) / (no. of injections prescribed)

. Treatment compliance for subjects will be summarized for subjects for each treatment period of the study.

2.4.2 Prior & concomitant medications

Concomitant medications entered into the database will be coded using the World Health Organization Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system.

Prior and concomitant medications will be summarized by treatment group in separate tables for the safety set unless otherwise specified. Medications will be presented in alphabetical order, by ATC codes and grouped by *anatomical main group* (the 1st level of the ATC codes). Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code, at least one drug in a particular anatomical main group and any Methotrexate or any Cortcosteroids.

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

Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taken.

Prior & concomitant procedures will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology. Prior and concomitant procedures will be summarized by treatment group for the safety set unless otherwise specified and will be displayed by treatment period.

Prior psoriasis-psoriatic arthritis therapies details will also be listed for each patient and summized by therapy type (biologic systemic, non-biological systemic therapy {Methotrexate, Corticosteroid, NSAID and DMARDs}, topical, phototherapy and photo chemotherapy).

The number and percentage of subjects receiving prior and concomitant therapies from the *Prior Psoriasis-Psoriatic Arthritis Therapy eCRF* will be presented by randomized treatment group as well as the reasons for stopping their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other).

2.5 Analysis of the primary objective

The primary objective is 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 inadequate response (IR) to non-biologic DMARDs (reference Appendix 5.7 for further details).

2.5.1 Primary endpoint

The primary analysis variable is the change from baseline in GLOESS over 12 weeks.

The analysis of the primary efficacy variable and all other efficacy variables will be based on the FAS. All efficacy variables will be summarized using descriptive statistics.

2.5.2 Statistical hypothesis, model, 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 ± MTX (and non-biologic DMARDs) 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 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).

2.5.3 Handling of missing values/censoring/discontinuations

The 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.

2.5.4 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, the treatment of missing data and protocol deviations/audit findings.

[redacted]

The GLOESS score will be revised to account for a small number of composite PDUS scores that are not in agreement with the definition of synovitis that power doppler alone does not mean synovitis (D'Agostino (2016), Terslev L (2016)). This endpoint will be named 'GLOESS revised (Definition 2).' and the primary analysis (MMRM) will be repeated on the revised definition.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

The key secondary efficacy variables are as follows:

- Proportion of patients with ACR 20 response at Week 12 in each treatment arm.
- Proportion of patients with ACR 50 response at Week 12 in each treatment arm.
- Change in SPARCC enthesitis index from Baseline to Week 12 in each treatment arm.

2.6.1.1 American College of Rheumatology response

The ACR response (reference Appendix 5.9 for details) 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.

2.6.1.2 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 1.

Table 1: 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

Tenderness at each site is quantified on a dichotomous basis: 0= non-tender and 1= tender. The sum of scores from each site is calculated to give a range of a total score for the index from 0 to 16.

2.6.2 Statistical hypothesis, model, and method of analysis

The following null 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:

- H_1: secukinumab s.c. is not different to placebo regimen with respect to the change in GLOESS from Baseline to Week 12.

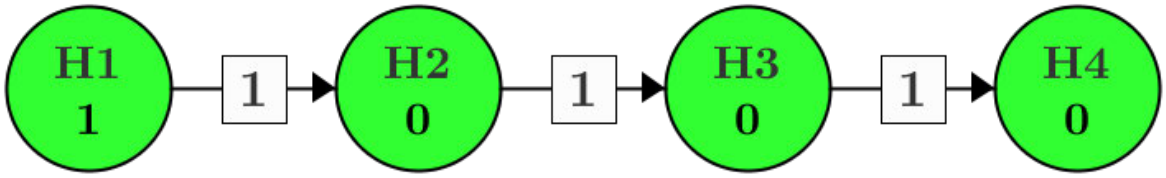
See section 2.5.2 for details.

Key secondary objectives:

- H_2: secukinumab is not different to placebo regimen with respect to ACR 20 response at Week 12.
- H_3: secukinumab s.c. is not different to placebo regimen with respect to ACR 50 response at Week 12.
- H_4: 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 1).

Figure 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. In cases where separation is a concern for secondary endpoint at Week 12 an exact logistic regression model will be applied to all visits. To ensure convergence, this model will not include any continuous covariates. When exactlogistic regression is unable to be implemented then Fisher's exact test will be applied.In this case no odds ratios or confidence inervals can be estimated but p-values may be calculated.

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. In cases where separation is a concern for secondary endpoint at Week 12 an exact logistic regression model will be applied to all visits. To ensure convergence, this model will not include any continuous covariates. When exactlogistic regression is unable to be implemented then Fisher's exact test will be applied.In this case no odds ratios or confidence inervals can be estimated but p-values may be calculated.

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.

2.6.3 Handling of missing values/discontinuations

Missing data for the ACR 20 response and other binary efficacy variables (e.g. ACR 50, ACR 70, [redacted]PASI 75, PASI 90, PASI 100) for data up to 12 weeks (Week 12) will be handle[redacted]llows:

- 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.

2.6.4 Supportive analyses

[redacted]

Non responder imputation will be extended through to week 52 for ACR20, ACR 50, and ACR 70.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

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 12 for each of the 5 targeted entheses.

2.7.2 Statistical hypothesis, model, and method of analysis

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 for both definitions of enthesitis score at a site level (see section 5.11).

2.7.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed for the secondary efficacy endpoints.

2.8 Other efficacy variables/Exploratory analysis

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

[redacted]

- The response of ACR 20, ACR 50, ACR 70, PASI 75, PASI 90, PASI 100, [redacted]
- Change from Baseline in ACR components to week 12 [redacted]:
  - 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.

[redacted]

All results from the exploratory efficacy analyses will be interpreted descriptively.

For the double blind period;

- Continuous variables outlined above will be analysed using MMRM analysis analogous to that outlined for the primary efficacy variable, reference section 2.5.2 above.
- Binary outcome variables will be analyzed using logistic regression analogous to that outlined for the binary key secondary efficacy variables, reference section 2.6.2 above.

[redacted]

The Risk Ratio (RR) of ACR response in Secukinumab group / risk of ACR response in Placebo group will be determined. [redacted]

[redacted]

[redacted]

[redacted]

Non responder imputation will be extended through to week 52 for PASI 75, PASI 90 and PASI 100.

[redacted]

[redacted]

[redacted]

[redacted]

2.9 Safety analyses

All safety analyses will be based on the safety set. Only those visits which were pre-planned in the protocol will be reported in tables and figures for safety variables. All summaries will be performed on actual treatment recieved showing AEs observed up to the end of each Treatment period and the entire treatment period.

2.9.1 Adverse events (AEs)

Only Treatment-emergent AEs (TEAEs) will be summarized. Treatment-emergent AEs (TEAEs) are those AEs that 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.

TEAEs will be assigned to the last treatment received at the time of onset/worsening of AE. For summaries beyond treatment period 1, patients who switched from Placebo to Secukinumab will appear in both the population of patients for Placebo and Secukinumab (150 mg + 300 mg) treatment groups. If an AE occurred on the last day of treatment period 1 and the patient did not enter treatment period 2 it will be included as a TEAE in the treatment period 1.

Adverse events will also be reported according to MedDRA. The MedDRA version used for reporting the study will be described in a footnote.

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 particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. 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.

The incidence of AEs will be presented per 100 patient years of exposure for the most frequent AEs ($\geq$ 2% in any group) and SAEs.

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

A graphical display of the crude rates within system organ classes will be presented. The placebo group will be displayed with a bar whereas dots will be used for secukinumab treatment groups.

Non-treatment emergent adverse events will be summarized as well. These adverse events occurred before the first dose of the study treatment. The crude incidence rate will be provided without treatment information.

Algorithms for date imputations will be provided in Appendix 5.1.2.

Exposure time-adjusted incidence rates including 95% CIs will be presented for the entire treatment period. A graphical display of the crude rates and exposure-adjusted incidence rates will be presented for all AEs and SAEs by SOC.

In addition, for the legal requirements of clinicaltrials.gov and EudraCT, 2 required tables on TEAEs which are not SAEs with an incidence greater than 2% and on treatment emergent AEs and SAEs suspected to be related to study treatment will be provided by primary SOC and PT on Safety set population.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same primary SOC and PT:

- A single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- More than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE/SAE suspected to be related to study treatment/non-SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.9.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest (AESI) of the Safety Profiling Plan (SPP) and the Risk Management Plan will be identified through an extraction from the electronic Case Retrieval Strategy database. The extraction will be performed by selecting those records where the drug name is AIN457 and the indication is psoriasis, psoriatic arthritis and ankylosing spondylitis.

To this end, the following events will be considered as adverse events of special interest:

- Major adverse cardiovascular events (MACE): identified per Novartis MedDra Query (NMQ) “MACE (MI, Stroke, Cardiovascular death)”
- Inflammatory bowel disease: identified per NMQ narrow “Inflammatory bowel disease”
- Infections and infestations: identified per SOC “Infections and infestations”
    - Fungal infectious disorders : identified per HLGT
    - Staphylococcal infections : identified per HLGT

- Herpes viral infections : identified per HLGT
- Mycobacterial infectious disorders : identified per HLGT
- Central nervous system infections and inflammations : identified per HLGT
- Oesophageal candidiasis : identified per SMQ narrow
- Infections of skin structures : identified per NMQ1
- Infectious pneumonia : identified per NMQ1
- Opportunistic infections : identified per NMQ1

- Malignancy: identified per NMQ “Malignant or unspecified tumours (SMQ excluding BCC and SCC)” or per SMQ for “Malignant or unspecified tumours

(SMQ)", "Skin tumours malignant and unspecified" or "Non-melanoma skin cancer (BCC and SCC)

- Hypersensitivity: identified per SMQ narrow "Hypersensitivity"
- Neutropenia : identified per NMQ
- Suicidal ideation and behaviour : identified per Suicide/self-injury (SMQ)
- Interactions with live vaccines : identified per HLT "Vaccination related complications"
- Hepatitis B reactivation : identified per HLT "Hepatitis viral infections"

The crude rates for AESIs will be summarized. In addition, listings will be provided presenting which subjects experienced which risk.

Important note: For the evaluation of AESIs risks, primary and secondary system organ classes of the MedDRA dictionary will be considered.

2.9.2 Deaths

A separate summary of adverse events causing death will be presented by treatment group.

2.9.3 Liver Safety

A summary of liver events will be presented by treatment group.

2.9.4 Renal Safety

A summary of renal events will be presented by treatment group.

2.9.5 Laboratory data

The summary of laboratory evaluations will be presented for 3 groups of laboratory tests (hematology, serum chemistry and urinalysis). For urinalysis, frequency tables will be presented. Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by visit, 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 (maximum decrease and maximum increase) 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.

Individual subject data listings will be provided for subjects with abnormal laboratory data.

Box plots may be presented for selected laboratory parameters (WBC, neutrophils (absolute count), AST, ALT and creatinine). These box plots would show the following location parameters: The bottom and top edges of the box will represent the 25th and 75th percentile, respectively. The center horizontal line of the box will represent the median. Lower and upper whiskers will reach to the 10th and 90th percentile, respectively. Values below the 10th percentile and above the 90th percentile will be presented by circles. Mean values will also be represented in the plot and connected with a line.

2.9.6 Other safety data

2.9.6.1 ECG and cardiac imaging data

Not applicable

2.9.6.2 Immunogenicity

Summary statistics will be provided for the percentage of patients with blood samples for immunogenicity (anti-AIN457 antibodies).

2.9.6.3 Pregnancy tests

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

2.9.6.4 QuantiFERON TB-Gold test

A listing of the QuantiFERON TB-Gold test results will be presented by treatment group.

2.9.6.5 PPD skin test

A listing of the PPD skin test results will be presented by treatment group.

2.9.6.6 Local tolerability (injection site reactions)

A separate summary of injection site reactions will be presented by treatment group.

2.9.6.7 Antibodies

A listing of the anti-CCP antibodies, Rheumatoid Factor (RF), Antinuclear antibodies (ANA) and anti-dsDNA antibodies will also be listed by visit and treatment group.

2.9.6.8 Chest X-ray/MRI

A listing of the chest X-ray/MRI results will be presented by treatment group.

2.9.7 Additional parameters

2.9.7.1 Physical examination

Not applicable.

2.9.7.2 Vital signs

Analysis of vital sign measurements (systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and pulse (bpm)) using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

The number and percentage of subjects with newly occurring notable vital signs will be presented, by treatment period. Criteria for notable vital sign abnormalities are provided in Table 2 below.

Table 3: Criteria for notable vital sign abnormalities

Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg)	>= 140 mmHg or < 90 mmHg
Diastolic blood pressure (mmHg)	>=90 mmHg or <60 mmHg
Pulse (bpm)	> 100 bpm or <60 bpm

A blood pressure indicative of prehypertension (systolic 120 to < 140 mmHg and/or diastolic 80 to < 90 mmHg) will not be regarded as notable.

2.10 Pharmacokinetic endpoints

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

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.

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

2.11 PD and PK/PD analyses

Not applicable

2.12 Patient-reported outcomes

Not applicable

2.13 Biomarkers

Not applicable.

2.15 Interim analysis

Prior to the Week 52 database lock and end of study reporting there are 3 other analyses planned; a blinded sample size re-estimation (SSR), a Week 12 and a Week 24 analysis.

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.

3 Sample size calculation

3.1 Determination of sample size

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 PDUSscore 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.

4 Change to protocol specified analyses

[redacted]

- The secondary endpoint Change in OMERACT enthesitis score from Baseline to Week 8 for each of the 5 targeted entheses will be updated to change to week 12 to align with the secondary objective "To evaluate the therapeutic effect of secukinumab versus placebo on enthesitis at Week 12 using the OMERACT enthesitis score for each affected enthesis"

[redacted]

[redacted]

- PASI 100 will be summarised alongside PASI 75 and PASI 90.
- ACR 20, ACR 50 and ACR 70 will also be analysed at each timepoint until the end of study [redacted] along with Risk Ratios
- Week 12 interim analysis will be known as primary analysis.
- All screened patients analysis set added for disposition summary.

- [redacted]
- [redacted]
- Non-biologic prior and concomitant medications such as NSAIDs, MTX, Corticosteroids will be classified according to a coding file provided by the medical lead.
- Rules for deriving synovitis composite score were refined to include all permutations of the component data.
- The scoring of PDUS Enthesitis has been updated due to recently published findings that highlight the differences related to B Mode and Doppler. Different scenarios must be explored to develop a global OMERACT enthestis score at the patient level.
- [redacted]
- Non responder imputation (NRI) will be extended up to Week 52 for ACR 20/50/70 & PASI 75/90/100 as supportive analysis to determine the robustness of the data. NRI will also be conducted on the following clinical outcomes; [redacted]
- [redacted]
- Proportion of patients with a presence of PDUS synovitis (Composite PDUS, SH and PD) will be summarised over time.
- [redacted]

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Incomplete Start Date:

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first doing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed, the corresponding AE will be included as TEAE.

Incomplete Stop Date: If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.

• If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

5.1.3 Concomitant medication date imputation

Table 3 below should be used to determine whether medications are concomitant or not. If a medication is considered concomitant it should be reported in each treatment period in which it is administered. The rules below for determining if a medication is concomitant should be applied to determine if the medication is concomitant within a particular period by using the start and end dates of the treatment period rather than overall start and end dates of study medication. The phases are defined in Section 2.1.1. In the event that the medication could have potentially started in either phase then it should be considered concomitant in both.

Table 4: Concomitant medication date imputation

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= study med end date, assign as concomitant If start date > study med end date, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= study med end date, assign as concomitant If start date > study med end date, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

5.1.3.1 Prior therapies date imputation

Refer to Section 5.1.3 above.

5.1.3.2 Post therapies date imputation

Refer to Section 5.1.3 above.

5.1.3.3 Other imputations

Not applicable.

5.2 AEs coding/grading

The verbatim term recorded on CRF will be identified as adverse event and will be coded by primary system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 and above.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Assessment windows, baseline and post baseline definitions, missing data handling

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 of the protocol.

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.

Assessment windows

No assessment windows have been defined for this study. Visit windows are described below.

Visits windows

Visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in Table 4. In this table, the days are counted since the first dose of study treatment (study days) for safety and efficacy assessments. These visit windows apply to measurements taken at every visit. For assessments collected less oftendifferent visit windows will be applied as detailed below.

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 4* visit of a subject is delayed and occurs on Day 46 instead of on Day 29, say, it will be re-aligned to visit window *Week 8*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

Of note, subjects are allowed to have gaps in visits.

Table 5-1: Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 days to Day 1*
Week 1	1	8	Day 2-11
Week 2	2	15	Day 12-18
Week 3	3	22	Day 19-25
Week 4	4	29	Day 26-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-99
Week 16	16	113	Day 100-127
Week 20	20	141	Day 128-155
Week 24	24	169	Day 156-211
Week 36	36	253	Day 212-309
Week 52	52	365	Day 310-379
Week 56	56	393	Day 380-421
Week 64	64	449	Day 422-463

* Baseline measurement before the first drug administration for safety assessments and before the randomization for efficacy assessments. The days are counted since the first dose of study treatment for safety assessments, and the days are counted since the date of randomization for efficacy assessments.

For parameters which are not collected at every visit, visit windows defined in Table 4 will be combined. For example, if a parameter is measured at Week 12 and Week 24 only, Week 12 visit window will extend from Day 2 to Day 99 (combining Week 1 to Week 12 visit windows), Week 24 will extend from Day 89 to Day 211 (combining Week 13 to Week 24). If more than one assessment falls into the interval, the rules defined below are applied.

Assessments from one treatment period will not be considered for another treatment period. For example, if a Week 13 (scheduled visit) measurement falls into the Week 12 visit window, this measurement would not be analyzed as treatment period 1 value.

Of note, for subjects who discontinue in treatment period 1, i.e. not moving into treatment period 2, efficacy measurements taken in follow-up period would still be considered for the treatment period 1.

The analysis visit will be used for listing of visit and treatment period for safety data. If a visit falls after the last visit window (after Day 463) it is not assigned an analysis visit and will be listed under label “After Week 64”.

The administration of study drug at Week 28, 32, 40, 44, and 48 is not in relation to a study visit. For exposure data, a specific assessment window for those weeks is used in order to account for the home administrations at those weeks.

Table 5-2: Drug administration windows for scheduled visits of Exposure Data

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 days to Day 1*
Week 1	1	8	Day 2-11
Week 2	2	15	Day 12-18
Week 3	3	22	Day 19-25
Week 4	4	29	Day 26-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-99
Week 16	16	113	Day 100-127
Week 20	20	141	Day 128-155
Week 24	24	169	Day 156-183
Week 28	28	197	Day 184-211
Week 32	32	225	Day 212-239
Week 36	36	253	Day 240-267
Week 40	40	281	Day 268-295
Week 44	44	309	Day 296-323
Week 48	48	337	Day 324-351
Week 52	52	365	>= 352 Days

Multiple assessments within visit windows

When there are *multiple assessments* in a particular visit window, the following rules are applied to select one value "representing" the subject in summary statistics in a visit window (See Table 5).

For baseline assessment definition see Section 2.1.1. For post-baseline visit windows the following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen)
- for *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, *worst* case is always well defined (e.g., for urine protein values "+" and "++", the worst case is defined as "++")
- in case qualitative variables are based on quantitative variables, e.g. PASI 75 response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable

Table 6: Rules for selecting values for analysis

Timing of measurement	Type of data	Rule
Baseline	All data	See Section 2.1.1
Post-baseline efficacy	Continuous data	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used
Post-baseline efficacy	Categorical data	The most extreme (the worst) measurement in the window will be used. For example, among 'a little better' and 'moderately better' values 'a little better' value will be selected.
Post-baseline safety	Continuous data	The (non-missing) measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurments are taken on the same day then select the first one (using the time). If two measurements are taken on the same date/time then use the first visit number (assuming this is the planned visit).
Post-baseline safety	Categorical data	The most extreme (the worst) measurement in the window will be used. For example, among 'a little better' and 'moderately better' values 'a little better' value will be selected

5.5 Statistical models

5.5.1 Primary 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.

The model to be tested is as follows:-

Change from baseline in GLOESS = Treatment + center + analysis visit + weight + baseline GLOESS + Treatment * analysis visit.

The procedure PROC MIXED will be used to perform the MMRM analysis. Treatment regimen, center and analysis visit will be set as class variables. The model statement will be based on the formula outlined above. The repeated statement of PROC MIXED will set analysis visit as the repeated variable and the type option will set the convergence method. An unstructured covariance structure will be assumed for this model (type=UN). If the model does not converge, the compound symmetry covariance structure will be used (type=CS). The data will be assumed to be missing at random (MAR). The overall method will be set to REML.

From this analysis, the adjusted changes for each treatment group, the difference between the adjusted changes (secukinumab group vs placebo), 95% confidence interval around the difference and 1-sided p-value will be calculated for each visit.

5.5.2 Key secondary analysis

The key secondary objectives:

- H_2: secukinumab is not different to placebo regimen with respect to ACR 20 response at Week 12.
- H_3: secukinumab s.c. is not different to placebo regimen with respect to ACR 50 response at Week 12.
- H_4: secukinumab s.c. is not different to placebo regimen with respect to the change in SPARCC enthesitis index from Baseline to Week 12.

H2 will be tested as follows:-

ACR 20 at Week 12 = Treatment + weight.

The procedure PROC LOGISTIC will be used to perform the logistic regression analysis. Treatment regimen will be set as a class variable. The model statement will be based on the formula outlined above. Reference coding will be used in the model. The odds ratios will be computed for comparison of secukinumab versus placebo using the logistic regression model fitted. If the initial model does not converge Firth's penalized maximum likelihood estimation method will be used.

H3 will be analysed analogous to H2 above.

H4 will be analysed analogous to the primary efficacy variable.

5.6 Rule of exclusion criteria of analysis sets

Table 7 Subject Classification

Analysis Set / Subgroup of interest	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
Randomized set	INCL01	Not randomized; Mistakenly randomized
FAS	INCL01	Not in RAN; Study treatment not assigned;

Analysis Set / Subgroup of interest	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
Safety set	INCL01	No study drug taken
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

5.7 Power Doppler Ultrasonography

Power Doppler and Grayscale ultrasound (PDUS) is a 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 [redacted].

The Outcome Measures in Rheumatology and the European League Against Rheumatism (OMERACT-EULAR) Ultrasound Task Force has developed a composite scoring system (the OMERACT-EULAR global synovitis score (GLOESS) as measured using PDUS) to detect and score synovitis at patient level. This score combines Grayscale-assessed synovial hyperplasia with an intra-synovial Power Doppler signal for evaluating synovial activity at joint level.

PDUS evaluation will be performed at each joint site out of 48 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 (PID) 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).

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 6 targeted entheses will be scored in terms of inflammatory and morphological components according to the OMERACT enthesitis composite semi-quantitative scale (0 to 3).

5.8 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: 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.

5.9 American College of Rheumatology measures and criteria of response

The ACR has seven criteria:-

Number of tender joints:

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

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".

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".

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.

High sensitivity C-reactive protein

The purpose of this assessment is to identify the presence of inflammation, to determine its severity, and to monitor response to treatment. As 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.

Patient's assessment of physical function

Health Assessment Questionnaire – HAQ-DI© (reference Appendix 5.13)

5.10 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

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 8).

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 8). 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.

Table 8: 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 i.e. B MODE=0 and Doppler=0
Grade 1 (minimal synovitis)	Minimal synovial hyperplasia and ≤ Grade 1 Power Doppler signal i.e. B MODE=1 and Doppler ≤1 OR B MODE=0 and Doppler=1 For revised GLOESS : Minimal synovial hyperplasia and ≤ Grade 1 Power Doppler signal i.e. B MODE=1 and Doppler ≤1
Grade 2 (moderate synovitis)	Moderate synovial hyperplasia and ≤ Grade 2 Power Doppler signal or minimal synovial hyperplasia and a Grade 2 Power Doppler signal i.e. B MODE=2 and Doppler ≤2 or B MODE≤2 and Doppler=2
Grade 3 (severe synovitis)	Severe synovial hyperplasia and ≤ Grade 3 Power Doppler signal or moderate synovial hyperplasia and a Grade 3 Power Doppler signal i.e. B MODE=3 and Doppler ≤3 or B MODE≤3 and Doppler=3
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)

Note: B MODE is hypoechoic synovial hypertrophy independently of the presence of effusion.

The revised GLOESS definition will also be known as GLOESS definition 2 with the original GLOESS derivation known as GLOESS definition 1.

Proportion of patients with a presence of PDUS synovitis (Composite PDUS, SH and PD) will be summarised over time.

5.11 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.

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.

Table 9: 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

Each affected enthesis out of 6 targeted entheses will be scored on inflammatory and morphological components according to the following formulae;

Total OMERACT (PDUS) enthesitis score Definition 1 : The sum of inflammation (Power Doppler: ranging from 0-3) and morphological (B mode: 0=absence, 1=presence) components
Total OMERACT (PDUS) enthesitis score Definition 2 : The inflammation component (Power Doppler: ranging from 0-3), independently of the B Mode.

The Global score at each assessment visit (i.e. the sum of the total score of each enthesis site involved) will be derived using the following formulae;

Global OMERACT (PDUS) enthesitis Definition 1 : Sum of the B-Mode (0=absence, 1=presence) and PD signal (0=absence,1,2,3, most severe ranking =3) across 6 sites on the right side on 6 sites on left side. The score will range from 0-48.

Global OMERACT (PDUS) enthesitis Definition 2 : Sum of the PD signal (0=absence,1,2,3, most severe ranking =3) across 6 sites on the right side and 6 sites on the left side. The score will range from 0-36.

[redacted]

[redacted]

[redacted]

5.13 Health assessment questionnaire

The Health Assessment Questionnaire (HAQ©) 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".

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-DI response is defined as an improvement of at least 0.35 score points compared to baseline (change ≤ -0.35).

5.14 PASI

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 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.

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 12 below.

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

T Psoriasis area and severity index scoring system

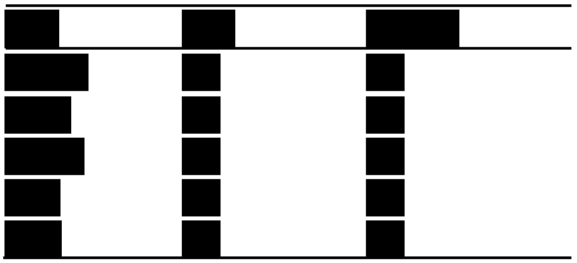
Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation, D)	Area score (based on true area %, A)*
Head (H)†	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe	0 = none 1 = slight 2 = moderate 3 = 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

Definitions of efficacy variables based on psoriasis area and severity index

- **PASI 75 response**: patients achieving ≥ 75% improvement (reduction) in PASI score compared to Baseline are defined as PASI 75 responders.
- **PASI 90 response**: patients achieving ≥ 90% improvement (reduction) in PASI score compared to Baseline are defined as PASI 90 responders.
- **PASI 100 response**: patients achieving ≥ 100% improvement (reduction) in PASI score compared to Baseline are defined as PASI 100 responders.

[redacted]



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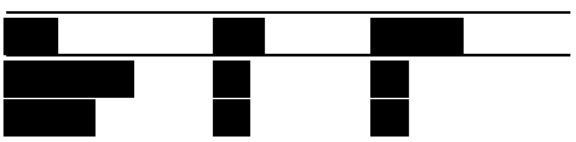

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