NOVARTIS

US Clinical Development & Medical Affairs - General Medicine

AIN457/Secukinumab

Clinical Trial Protocol CAIN457FUS01 / NCT02798211

A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of secukinumab 300 mg and 150 mg in adult patients with active psoriatic arthritis after 16 weeks of treatment compared to placebo and to assess the safety, tolerability and efficacy up to 52 weeks

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
ANCOVA	analysis of covariance
Anti-CCP	Anti-cyclic citrullinated peptide
AS	Ankylosing Spondylitis
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
BSA	Body Surface Area
BL	Baseline
CASPAR	Classification criteria for Psoriatic Arthritis
CRF	Case Report/Record Form (paper or electronic)
CRP	C-reactive protein
CTC	Common Toxicity Criteria
[redacted]	[redacted]
DAS	Disease Activity Score
DLQI	Dermatology Life Quality Index
DMARD	Disease Modifying Anti-rheumatic Drug
DS&E	Drug Safety & Epidemiology
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA/EMEA	European Medicines (Evaluation) Agency
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
[redacted]	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ-DI©	Health Assessment Questionnaire – Disability Index
HRQoL	Health-related Quality of Life
hsCRP	High sensitivity C-Reactive Protein
IEC	Independent Ethics Committee
IGA mod 2011	Investigator's Global Assessment modified 2011
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra Uterine Device
IUS	Intra Uterine System
i.v.	intravenous(ly)
[redacted]	[redacted]
LFT	Liver function test

[redacted]

LOCF	last-observation-carried-forward
MCS	Mental Component Summary
MDA	Minimal Disease Activity
[redacted]	[redacted]
MedDRA	Medical dictionary for regulatory activities
mmHg	Millimeter mercury
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PBO	Placebo
PCS	Physical Component Summary
PFS	Prefilled syringe
PK/PD	Pharmacokinetic/Pharmacodynamic
PoC	Proof of Concept
PPD	Purified protein derivative
PRN	Pro re nata (as required)
PRO	Patient Reported Outcome
PsA	Psoriatic arthritis
[redacted]	[redacted]
QoL	Quality of Life
RBC	Red blood cell
RF	Rheumatoid factor
SAE	Serious adverse event
s.c.	Subcutaneous(ly)
SCR	Screening
SF-12	Medical Outcome Short Form (12) Health Survey
SJC	Swollen Joint Count
SpA	Spondyloarthritis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TJC	Tender Joint Count
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell
WHO	World Health Organization
[redacted]	[redacted]

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Premature subject withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

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Amendment 2

Rationale for Amendment

The purpose for Amendment 2 is to update Table 6-1 (Assessment Schedule) to include the visits at which the Enthesitis Evaluation must be done.

Amendment 1

Rationale for Amendment

The purpose for Amendment 1 is to update the following Sections and Tables.

- **Section 4.1:** Inclusion criteria number four (4) was updated to justify the need for a baseline skin scoring accordingly. Therefore, it was reworded to: a target psoriatic skin lesion and a PASI score of 1 or greater.

- **Section 5.2:** Patients will receive treatment up to Week 48 and no treatment will be administered at the EOT Visit/Week 52.

- **Section 5.5.8 and Table 5.1:** The table was rearranged to clarify that no biologics are allowed in the study. This is to prevent any further confusion that was observed since the study launched.

- **Section 6:** Previous version required a 4 week waiting time even for those patients who are treatment naïve, and do not need a washout or repeat assessments. The related section of FUTURE 5 global protocol is adapted to prevent a 4 week waiting period for those patients. Screening will now be more flexible in duration up to 8 weeks prior to randomization based on the time required to wash out prior anti-rheumatic medications. Patients that do not require a washout can proceed onto the baseline visit once all inclusion criteria and none of the exclusion criteria are met.

- **Section 6.4.2:** Was updated to remove the Independent Joint Assessor requirement. This is the first study evaluating various typical findings for PsA such as TJC, SJC, PASI, IGA, enthesitis, dactylitis [redacted]. Therefore, it is unlikely for the site personnel to have independent assessors for each evaluation. In order to best reflect the current standard of practice, it is per the Investigator's discretion to decide who will be performing the evaluations.

[redacted]

[redacted]

- **Section 6.4.6:** Updated to emphasize the importance that the Erythrocyte Sedimentation Rate test must be performed locally.

- **Section 6.5.6:** Updated to include that a serum β-hCG test will be performed in all women of child bearing potential at Screening Visit 2; and a local urine pregnancy tests will be performed at the specified visits as indicated in Table 6-1.

- **Appendix 12.10:** The PROs Guidelines for the SitePad have been updated.

[redacted]

Protocol summary

Protocol number	CAIN457FUS01
Title	A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of secukinumab 300 mg and 150 mg in adult patients with active psoriatic arthritis after 16 weeks of treatment compared to placebo and to assess the safety, tolerability and efficacy up to 52 weeks
Brief title	Study to evaluate the safety and efficacy of Cosentyx® (secukinumab) 300 mg and 150 mg in adult patients with active psoriatic arthritis (PsA) after 16 weeks of treatment compared to placebo
Sponsor and Clinical Phase	Novartis / Phase IV
Investigation type	Drug: Biological
Study type	Interventional
Purpose and rationale	The purpose of this study is to provide 16 week safety, efficacy and tolerability data in adult biologic naïve PsA patients with target skin lesions and evaluate the effect of secukinumab on PsA specific clinical findings such as dactylitis, enthesitis and psoriatic lesions. The study will also evaluate the early efficacy of the treatment at the first scheduled clinical visit after starting a treatment (i.e., at Week 4) and long term safety and efficacy up to 52 weeks
Primary Objective(s)	To demonstrate that the efficacy of secukinumab 300 mg at Week 16 is superior to placebo in adult patients with active PsA based on the proportion of patients achieving an American College of Rheumatology 20 (ACR20) response.
Secondary Objectives	To evaluate: • The efficacy of secukinumab 150 mg compared to placebo at Week 16 in patients with active PsA based on the proportion of patients achieving an American College of Rheumatology 20 (ACR20) response. • The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients with dactylitis in the subset of patients who have dactylitis at baseline. • The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients with enthesitis in the subset of patients who have enthesitis at baseline. • The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 in subset of patients with active PsA and number of tender and swollen joints less than 10 at baseline based on the proportion of patients achieving ACR20, ACR50, and ACR70 responses • The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients achieving ACR50 and ACR70 responses. • The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients achieving Minimal Disease Activity (5 of the following 7 criteria: ≤1 tender joint, ≤1 swollen joint, PASI ≤1 or IGA mod 2011 ≤1,

	patient assessment of pain (0-100 Visual Analog Scale (VAS)) ≤15, patient global assessment of disease (VAS) ≤20, HAQ-DI ≤0.5, tender entheseal points ≤1). • The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients achieving a PASI75, PASI90, and PASI100 responses • The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the change from baseline in DAS28-CRP. • The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the change from baseline in Psoriatic Arthritis Disease Activity Score (PASDAS). • The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the change from baseline in SF12. • The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the change from baseline in HAQ-DI. • The overall safety and tolerability of secukinumab 300 mg and 150 mg compared with placebo as assessed by vital signs, clinical laboratory values, and adverse events (AE) monitoring.
Study design	This study uses a multicenter, randomized, double-blind, placebo-controlled, parallel-group design. Approximately 250 adult patients (in 2:2:1 ratio; 100 secukinumab 300 mg, 100 secukinumab 150 mg and 50 placebo) with active PsA and a target skin lesion and a PASI score of 1 or greater will be randomized from approximately 65 investigative sites in the United States. Screening will be flexible in duration based on the time required to wash out prior anti-rheumatic medications and have a duration of up to 8 weeks before randomization, followed by a treatment period up to Week 52. **Patients that do not require a washout can proceed onto the baseline visit once all inclusion criteria and none of the exclusion criteria are met.** At baseline (BL), patients whose eligibility is confirmed will be randomized to one of three treatment groups and will enter the Placebo Controlled Treatment Period. **<u>Treatment Period 1</u>** Treatment Period 1 is defined as the period from Randomization through Week 16 (prior to the Week 16 dose). At the start of Treatment Period 1, patients will be randomized via IRT in a 2:2:1 ratio to one of three treatment groups. • **Group 1**- **Secukinumab 300 mg**: secukinumab 300 mg (two s.c. injections of the 150 mg dose) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks. • **Group 2- Secukinumab 150 mg**: secukinumab 150 mg (one s.c. injection of the 150 mg dose and one s.c. injection of placebo) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and

[redacted]

	4), followed by dosing every four weeks.
	
	• **Group 3- Placebo**: placebo (two s.c. injection of 150 mg secukinumab placebo per dose) once per week for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.
	
	At each study treatment visit two s.c. injections in the form of PFS will be administered. This is necessary to maintain the blind, as secukinumab in PFS is available in either 1.0 mL (150 mg) or 2 x 1.0 mL (300mg). Placebo to secukinumab is also available in 1.0 mL to match the active drug.
	
	Rescue medication is not allowed until Week 16.
	
	Treatment Period 2
	• Patients receiving secukinumab 300 mg (**Group 1**) will continue to receive the same dose up to Week 48.
	• At Weeks 16, 28 and 40 patients on secukinumab 150 mg (**Group 2**) will be classified as responders (≥ 20% improvement from BL in both tender and swollen joint counts) or non-responders.
	  • At Weeks 16, 28 and 40 patients on secukinumab 150 mg (Group 2) who are responders will continue to receive secukinumab 150 mg (1.0 mL) plus placebo (1.0 mL) every 4 weeks until next evaluation of responder status at weeks 28 or 40.
	  • Patients who did not meet the responder criteria at Week 16, 28 or 40 will start receiving secukinumab 300 mg s.c. every 4 weeks and will continue this dose up to Week 48.
	• Patients on placebo (**Group 3**) regardless of their responder status will start receiving secukinumab 300 mg s.c. every 4 weeks from Week 16 up to Week 48.

Population	The study population will be comprised of approximately 250 patients who have passed screening assessments, comply with eligibility criteria and have provided written consent. • Male and female patients aged at minimum 18 at time of consent, with active PsA fulfilling the CASPAR criteria. • Patients must have symptoms for at least 6 months with moderate to severe PsA and must have ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 at BL (dactylitis of a digit counts as one joint each). • Patients must have a target skin lesion and a PASI score of 1 or greater. • Patients must report active disease despite current or previous NSAIDs and / or DMARDs. Concomitant therapy with MTX (≤25 mg/week) will be acceptable, if dose and route of administration have been stable for at least four weeks prior to the

[redacted]

	randomization visit. • Patients can be re-screened only once and re-screening study related procedures should not be performed prior to written re-consent by the subject. Mis-randomized Patients or discontinued patients cannot be re-screened. • Enrollment will stop as soon as the target number of randomized patients is reached.
Inclusion criteria	1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed 2. Male or non-pregnant, non-lactating female patients at least 18 years of age 3. Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have had at Baseline ≥ 3 tender joints out of 78 and ≥ 3 swollen joints out of 76 (dactylitis of a digit counts as one joint each) 4. A target skin psoriatic lesion and a PASI score of 1 or greater 5. RF and/or Anti-cyclic citrullinated peptide (antiCCP) antibodies negative at screening 6. Patients who are regularly taking NSAIDs as part of their PsA therapy are required to be on a stable dose for at least 2 weeks before study randomization and should remain on a stable dose up to Week 16 7. Patients taking corticosteroids should be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization and must remain on a stable dose up to Week 16 8. Patients taking MTX (≤ 25 mg/week) are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization and must remain on a stable dose up to study completion 9. Patients on MTX must be on folic acid supplementation at randomization 10. Patients who are on a DMARD other than MTX must discontinue the DMARD 4 weeks prior to randomization visit except for leflunomide, which should be discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed
Exclusion criteria	1. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician 2. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor 3. Use of any investigational drug and/or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug, whichever was longer 4. Ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, ultraviolet therapy) at randomization. The following wash out periods need to be observed:

[redacted]

	• Oral or topical retinoids 4 weeks • Photochemotherapy (e.g. Psoralen Plus Ultraviolet Light Therapy (PUVA)) 4 weeks • Phototherapy (UVA or UVB) 2 weeks • Topical skin treatments (except on face, eyes, scalp and genital area during screening, only corticosteroids with mild to moderate potency) 2 weeks 5. History of hypersensitivity to the study drug or its excipient or to drugs of similar chemical classes 6. Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization 7. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization 8. Patients who ever received biologic immunomodulating agents including those targeting TNFα, IL-6 and IL-12/23 investigational or approved 9. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., alemtuzumab, anti-CD4, anti-CD5, anti-CD3, anti-CD19) 10. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test 11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information. Effective contraception is defined in the Exclusion Criteria in Section 4.2. 12. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy 13. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy 14. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure [New York Heart Association status of class III or IV], uncontrolled diabetes 15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. The investigator should be guided by the following criteria: Any single parameter should not exceed 2 × upper limit of normal (ULN). a. A single parameter elevated up to and including 2 × ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out lab error b. If the total bilirubin concentration is increased above 2 × ULN,

[redacted]

	total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 µmol/L) 16. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6µmol/L) 17. Screening total White Blood Cells (WBC) count <3,000/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL (85g/L) 18. Active systemic infections during the last two weeks (exception: common cold) prior to randomization 19. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive Purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5mm or according to local practice/guidelines) or a positive QuantiFERON tuberculosis (TB)-Gold test as indicated in the assessment schedule. Patients with a positive test may participate in the study if further work-up (according to local practice/guidelines) established conclusively that the subject had no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated 20. Known infection with human immunodeficiency virus, hepatitis B or hepatitis C at screening or randomization 21. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed) 22. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial 23. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins) 24. Any medical or psychiatric condition which, in the investigator's opinion, precludes the participant from adhering to the protocol or completing the study per protocol 25. Donation or loss of 400 mL or more of blood within 8 weeks before randomization 26. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization 27. Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization
Investigational and reference therapy	**Treatment Period 1** • **Group 1**- **Secukinumab 300 mg**: secukinumab 300 mg (two s.c. injections of the 150 mg dose) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.

	• **Group 2- Secukinumab 150 mg**: secukinumab 150 mg (one s.c. injection of the 150 mg dose and one s.c. injection of placebo) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.
	• **Group 3- Placebo**: placebo (two s.c. injection of 150 mg secukinumab placebo per dose) once per week for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.
	
	<u>Treatment Period 2</u>
	• Patients receiving secukinumab 300 mg (**Group 1**) will continue to receive the same dose up to Week 48.
	• At Weeks 16, 28 and 40 patients on secukinumab 150 mg (**Group 2**) will be classified as responders (≥ 20% improvement from BL in both tender and swollen joint counts) or non-responders.
	  • At Weeks 16, 28 and 40 patients on secukinumab 150 mg (Group 2) who are responders will continue to receive secukinumab 150 mg (1.0 mL) plus placebo (1.0 mL) every 4 weeks until next evaluation of responder status at Weeks 28 or 40.
	  • Patients who did not meet the responder criteria at Week 16, 28 or 40 will start receiving secukinumab 300 mg s.c. every 4 weeks and will continue this dose up to Week 48.
	• Patients on placebo (**Group 3**) regardless of their responder status will start receiving secukinumab 300 mg s.c. every 4 weeks from Week 16 up to Week 48.

Efficacy assessments	• ACR20, ACR50, ACR70 responses • Tender 78 joint count and swollen 76 joint count • • Patient's Assessment of PsA pain intensity • Patient's global assessment of disease activity (VAS) • Health Assessment Questionnaire (HAQ-DI) • SF-12 [redacted] • Physician's global assessment of disease activity (VAS) • High Sensitivity C-reactive protein (hsCRP) • Erythrocyte sedimentation rate (ESR) • PASI • DAS28 and EULAR • PASDAS • Minimal Disease Activity

[redacted]

	[redacted] • IGA mod 2011 • Physician's assessment of nail disease (VAS)
Safety assessments	• Evaluation of AE/SAE's • Physical examination • Vital signs • Height and weight • QuantiFERON TB-Gold test or PPD skin test • Electrocardiogram • Local tolerability (Injection site reactions) • Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis) • Pregnancy and assessment of fertility • Tolerability of secukinumab
Other assessments	Quality of Life questionnaires/ Patient reported outcomes (PROs)
Data analysis	A designated Contract Research Organization will perform the statistical analysis. Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05. The following analysis sets will be used for the statistical reporting and analyses: Randomized Set: The Randomized Set includes all randomized patients. Safety Set: The Safety Set includes all patients who received at least one dose of study medication. Patients will be included in the analysis according to treatment received. Full Analysis Set: The Full Analysis Set comprises all patients to whom study medication has been assigned. Patients inappropriately randomized (e.g., IRT was called in error for randomization of a screen failed subject) will be excluded from this analysis set. Data will be summarized with respect to demographic and baseline characteristics of all patients, the subgroup of patients with dactylitis at baseline, and the subgroup of patients with enthesitis at baseline, for the Randomized Set and the Full Analysis Set. Efficacy, safety, and other data will be summarized. The primary efficacy variable is ACR20 response (yes, no). The primary analysis time point will be at Week 16. The primary efficacy variable will be analyzed at each time point using a logistic regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight as explanatory variables (Stokes, Davis, and Koch, 2012). The odds ratios for each dose of secukinumab versus placebo, 95% confidence intervals for the odds ratios, and p-values based on the fitted model will be reported. The primary analysis of the primary efficacy variable will be based on the

[redacted]

	Full Analysis Set. Patients who discontinued prematurely for any reason will be considered non-responders from the time they discontinued. Patients who do not have the required data to compute ACR response (i.e., tender and swollen joint counts and at least three of the five ACR domains) at baseline and at the specific time point will be classified as non-responders. The primary efficacy variable will also be analyzed at each time point for the Full Analysis Set using the Cochran-Mantel-Haenszel (CMH) test to compare each dose of secukinumab against placebo, adjusting for methotrexate usage at baseline (yes, no) (Stokes, Davis, and Koch, 2012). Two 95% confidence intervals for the difference between each dose of secukinumab versus placebo in the proportion of patients who are ACR20 responders will be calculated using the normal approximation to the binomial distribution. The secondary efficacy variables are the following: 1. Dactylitis (yes, no) 2. Enthesitis (yes, no) 3. ACR50 response (yes, no) 4. ACR70 response (yes, no) 5. Minimal Disease Activity (yes, no) 6. PASI75 response (yes, no) 7. PASI90 response (yes, no) 8. PASI100 (yes, no) 9. Change from baseline in DAS28-CRP 10. Change from baseline in PASDAS 11. Change from baseline in SF12 12. Change from baseline in HAQ-DI Two analyses of dactylitis and enthesitis (secondary efficacy variables 1 and 2) will be performed at each time point. For the first analysis, the data for the subgroup of patients who have dactylitis at baseline will be used (similarly for enthesitis) and the analysis of the binary response variable (yes, no) will be similar to the analysis of secondary efficacy variables 3-8 below. In the supporting analysis, the data for all patients will be used and an ordinal variable will be created based on presence (yes) or absence (no) of dactylitis at baseline and a post-baseline visit (similarly for enthesitis). The three categories for the ordinal variable will be no/no (category 1), no/yes and yes/no (category 2), and yes/yes (category 3). This ordinal response variable will be analyzed using a proportional odds regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight as explanatory variables (Stokes, Davis, and Koch, 2012). Secondary efficacy variables 3-8 will be analyzed at each time point using a logistic regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight as explanatory variables (Stokes, Davis, and Koch, 2012). Secondary efficacy variables 9-12 will be analyzed at each time point by

[redacted]

	an analysis of covariance (ANCOVA) model with treatment (3 treatment groups), baseline, methotrexate usage at baseline (yes, no), and body weight as explanatory variables. Missing data will be imputed using the last-observation-carried-forward (LOCF) method. Analyses of the secondary efficacy variables will be based on the Full Analysis Set. The assessment of safety will be based mainly on the frequency of adverse events and laboratory data. Other safety data (e.g., vital signs and special tests) will be considered, as appropriate. Analysis of safety data will be based on the Safety Set. The sample size was calculated based on the primary efficacy variable (i.e., ACR20 response) for the primary comparison (i.e., secukinumab 300 mg versus placebo). ACR20 response rates of 50% for secukinumab 300 mg and 20% for placebo (corresponding to an odds ratio of 4) at Week 16 were assumed, based on results from AIN457F2312 (FUTURE 2) study. Using a continuity-corrected chi-squared test, an allocation ratio of 2:1, a two-sided significance level of 0.05, and a power of 0.90, approximately 88 patients in secukinumab 300 mg group and 44 patients in placebo group will be needed (nQuery Advisor 7.0). Assuming a loss to follow-up rate of 10% and a 2:2:1 allocation ratio (secukinumab 300 mg: secukinumab 150 mg: placebo), the total number of randomized patients will be approximately 250 (100 on secukinumab 300 mg, 100 on secukinumab 150 mg, and 50 on placebo).
Key words	Active Psoriatic Arthritis, Subcutaneous secukinumab in prefilled syringes (PFS) , CASPAR

[redacted]

1 Introduction

1.1 Background

Psoriatic arthritis (PsA) is an immune-mediated chronic inflammatory disease belonging to the spectrum of conditions commonly referred to as spondyloarthritidies (SpA). While the various SpA may be diverse in their clinical presentations, common environmental as well as genetic factors associated with susceptibility to SpA are suspected (Turkiewicz and Moreland 2007). This latter notion was corroborated by findings in a large-scale single nucleotide polymorphism scan study, where interleukin (IL)-23R variants that were previously linked to Crohn's disease and psoriasis (diseases that may both co-exist with SpA) conferred risk to developing ankylosing spondylitis (AS) (Barrett et al 2008). Together, a common pathway, including the IL-23/IL-17 axis, may play a role in seronegative SpAs, including PsA.

PsA is a frequent and chronic immune-mediated disease encompassing a spectrum of overlapping clinical entities (Moll and Wright 1973). Up to 40% of patients with psoriasis will develop PsA, which is both more common and more severe than previously believed (Taylor et al 2006). PsA is also associated with significant morbidity and disability, and constitutes a major socioeconomic burden.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may improve symptoms in patients with mild PsA, but can worsen skin disease and be associated with an increased risk of cardiovascular side effects. Similarly, intra-articular injections of corticosteroids and low doses of systemic corticosteroids have been used with variable efficacy and significant side effects with chronic use. Disease-modifying anti-rheumatic drugs (DMARDs) are more typically used for PsA, and include methotrexate (MTX), sulfasalazine, cyclosporine, and leflunomide; however, these therapies may only partially control established disease (Mease 2008; Mease and Armstrong 2014). Biologic agents such as the tumor necrosis factor (TNF) inhibitors adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab are approved in patients with PsA to reduce joint disease activity, prevent structural damage, and improve function (Mease et al 2000, Mease et al 2005). However, TNF-inhibitor therapy may result in significant dose-limiting adverse effects, including the development of autoantibodies and the induction of a lupus-like syndrome.

Additional approved therapies for patients with PsA [redacted] Several lines of evidence support additional therapeutic pathways in PsA. Prominent T cell involvement occurs in the pathogenesis of PsA (Tassiulas et al 1999; Curran et al 2004; Mease and Armstrong 2014) and clinical trials have shown efficacy of T cell-targeted treatment that has included cyclosporine A, CTLA4-Ig, and alefacept. Despite available therapies for PsA, an unmet clinical need remains for agents that can be used singly or in combination with other therapies and provide effective short and long-term disease control especially on those PsA specific clinical findings such as dactylitis and enthesitis with favorable risk/benefit profiles.

IL-17 antagonism represents a novel therapeutic approach aimed at interference with the chronic inflammatory process by selectively targeting the predominant pro-inflammatory cytokine of the helper T17 cell subset. Additional effects of anti-IL-17 on bone homoeostasis

[redacted]

via receptor activator of nuclear factor kappa-B ligand (RANKL) and IL-1, upstream of TNFα,, can be inferred from animal studies (Koenders et al 2005). Assuming a potential role of IL-17 cells in the inflammatory infiltrate in PsA, it can be speculated that locally disturbed homeostasis of osteoclastogenic and osteoblastogenic mechanisms characteristic of PsA might be affected by IL-17 blockade, thus potentially providing a therapeutic advancement to effectively treat dactylitis and enthesitis in PsA.

Secukinumab (AIN457) is a high-affinity fully human monoclonal anti-human antibody that neutralizes IL-17A activity. IL-17A is the key cytokine in the newly discovered Th17 pathway that is believed to be an important mediator of autoimmunity. Neutralization of IL-17A has strong preclinical and clinical target validation.

A proof-of-concept study conducted in patients with PsA (CAIN457A2206) suggesting a clinically meaningful response for signs and symptoms up to Week 16. The efficacy of secukinumab in PsA patients is further supported by positive results for signs and symptoms (i.e. ACR20/50, PASI75/90), resolution of dactylitis, enthesitis and inhibition of radiologic damage at Week 24 obtained in a phase III study (CAIN457F2306; N=606) employing an intravenous (i.v.) loading regimen (3x10 mg/kg) of secukinumab Q2W followed by secukinumab s.c. 75 mg or 150 mg administered Q4W. In another phase III study (CAIN457F2312; N=397) secukinumab also demonstrated positive efficacy results superior to placebo in patients with PsA through most components of the arthritic and skin measures of signs and symptoms and physical function in a population comprised of 65% naïve to TNF-α inhibitors and 35% patients who were inadequate responders to a TNF-α inhibitor. Based on the results of these phase 3 trials, secukinumab received FDA approval in January 2016 for the treatment of active PsA and AS in adult patients. Therefore, treatment with secukinumab may result in improvement of symptoms and functional joint manifestations in afflicted patients.

The completed studies of secukinumab recruited both biologic exposed or naïve PsA patients with or without psoriatic skin lesions at baseline. Therefore a need for predefined prospective data exist for these different subgroups of patients which the precise effects of targeting IL-17A can be observed more clearly. The present study will evaluate the safety and efficacy of treatment with two doses of secukinumab compared with placebo in patients with active psoriatic arthritis and concomitant psoriasis who are naïve to biologic medications including tumor necrosis factor alpha (TNFα), IL-6 and IL-12/23 inhibitors. Also in the blinded long term extension period of this study, the effect of increasing the dose in non-responders after each evaluation every 12 weeks visit will provide valuable information regarding the correlation between the level of disease activity and IL-17A inhibition.

1.2 Purpose

The purpose of this study is to provide 16 week safety, efficacy and tolerability data in biologic naïve PsA patients with concomitant psoriatic skin lesions and evaluate the effect of secukinumab on PsA specific clinical findings such as dactylitis, enthesitis and psoriatic lesions. The study will also evaluate the early efficacy of the treatment at the first scheduled clinical visit after starting a treatment (i.e., at week 4) and investigate the remission status of all patients at each time points by evaluating the MDA, PASDAS and DAS28-CRP. This will be done in the blinded long term extension by increasing the dose to 300 mg in nonresponding

patients in 150 mg groups to confirm or support the role of higher IL-17A activity in PsA by evaluating the clinical response at every 12 weeks.

2 Study objectives

2.1 Primary objective(s)

To demonstrate that the efficacy of secukinumab 300 mg at Week 16 is superior to placebo in patients with active PsA based on the proportion of patients achieving an American College of Rheumatology 20 (ACR20) response.

2.2 Secondary objectives

To evaluate:

- The efficacy of secukinumab 150 mg compared to placebo at Week 16 in patients with active PsA based on the proportion of patients achieving an American College of Rheumatology 20 (ACR20) response.
- The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients with dactylitis in the subset of patients who have dactylitis at baseline.
- The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients with enthesitis in the subset of patients who have enthesitis at baseline.
- The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 in subset of patients with active PsA and number of tender and swollen joints less than 10 at baseline based on the proportion of patients achieving ACR20, ACR50, and ACR70 responses
- The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients achieving ACR50 and ACR70 responses.
- The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients achieving Minimal Disease Activity (5 of the following 7 criteria: ≤1 tender joint, ≤1 swollen joint, PASI ≤1 or IGA mod 2011 ≤1, patient assessment of pain (0-100 Visual Analog Scale (VAS)) ≤15, patient global assessment of disease (VAS) ≤20, HAQ-DI ≤0.5, tender entheseal points ≤1).
- The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients achieving a PASI75, PASI90, and PASI100 responses
- The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the change from baseline in DAS28-CRP.
- The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the change from baseline in Psoriatic Arthritis Disease Activity Score (PASDAS).
- The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the change from baseline in SF12.
- The efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the change from baseline in HAQ-DI.

[redacted]

- The overall safety and tolerability of secukinumab 300 mg and 150 mg compared with placebo as assessed by vital signs, clinical laboratory values, and adverse events (AE) monitoring.

3 Investigational plan

3.1 Study design

This study uses a multicenter, randomized, double-blind, placebo-controlled, parallel-group design. Approximately 250 adult patients (in 2:2:1 ratio; 100 secukinumab 300 mg, 100 secukinumab 150 mg and 50 placebo) with active PsA and a target skin lesion with PASI score of 1 or greater will be randomized from approximately 65 investigative sites in the United States.

Screening will be flexible in duration based on the time required to wash out prior anti-rheumatic medications and have a duration of up to 8 weeks before randomization, followed by a treatment period up to Week 52.

Patients that do not require a washout can proceed onto the baseline visit once all inclusion criteria and none of the exclusion criteria are met.

At baseline (BL), patients whose eligibility is confirmed will be randomized to one of three treatment groups and will enter the Placebo Controlled Treatment Period

Treatment Period 1

The Treatment Period 1 is defined as starting from Randomization through Week 16 (prior to the Week 16 dose). At the start of the Placebo-Controlled Treatment Period, patients will be randomized via IRT in a 2:2:1 ratio to one of three treatment groups (secukinumab 300 mg s.c., secukinumab 150 mg s.c. or placebo s.c.).

- **Group 1- Secukinumab 300 mg**: secukinumab 300 mg (two s.c. injections of the 150 mg dose) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.

- **Group 2- Secukinumab 150 mg**: secukinumab 150 mg (one s.c. injection of the 150 mg dose and one s.c. secukinumab injection of placebo) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.
- **Group 3- Placebo**: placebo (two s.c. injection of 150 mg secukinumab placebo per dose) once per week for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.

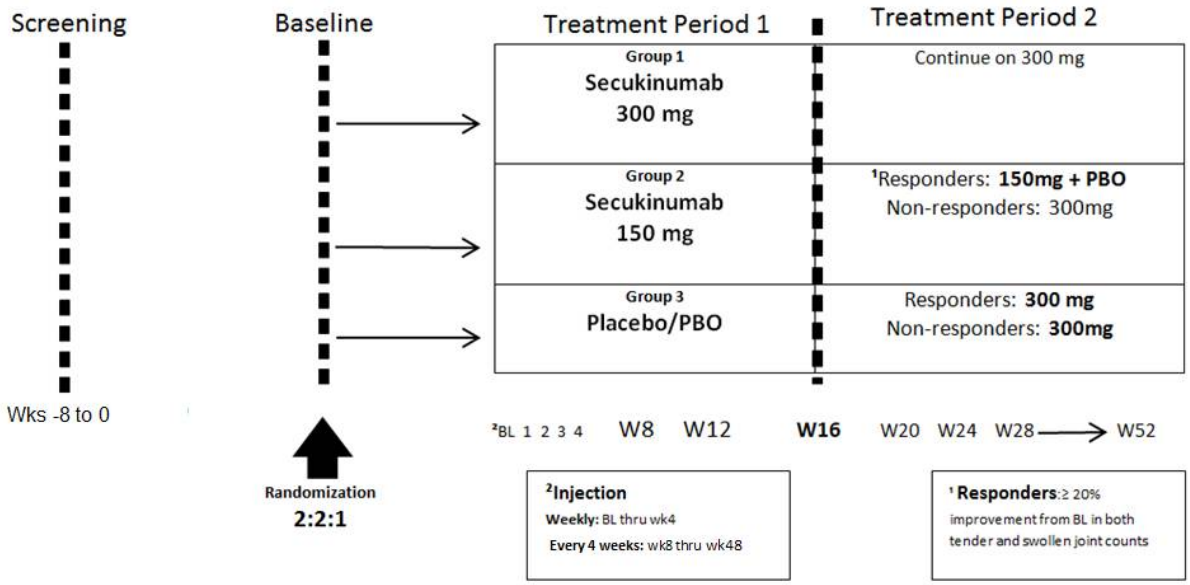
Treatment Period 2

- Patients receiving secukinumab 300 mg (**Group 1**) will continue to receive the same dose up to Week 48.
- At Weeks 16, 28 and 40 patients on secukinumab 150 mg (**Group 2**) will be classified as responders (≥ 20% improvement from BL in both tender and swollen joint counts) or non-responders.
  - At Weeks 16, 28 and 40 patients on secukinumab 150 mg (Group 2) who are responders will continue to receive secukinumab 150 mg (1.0 mL) plus placebo (1.0 mL) every 4 weeks until next evaluation of responder status at weeks 28 or 40.
  - Patients who did not meet the responder criteria at Week 16, 28 or 40 will start receiving secukinumab 300 mg s.c. every 4 weeks and will continue this dose up to Week 48.
- Patients on placebo (**Group 3**) regardless of their responder status will start receiving secukinumab 300 mg s.c. every 4 weeks from Week 16 up to Week 48.

Rescue medication will not be allowed during the day of the clinical visit and before completion of Week 16 assessments (Section 5.5.6). Although no subject will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, patients will be discontinued from the study if rescued with prohibited biologics (as described in (Section 5.5.8) and should obtain end of study assessments at the earliest possible date, provided consent to do so has not been withdrawn.

[redacted]

Figure 3-1 Study design



3.2 Rationale for study design

The double-blind, randomized, parallel-group placebo controlled design used in this study is aligned with Phase III trials of other biologics in this disease area and is in accordance with existing international guidelines. The treatment duration of the placebo group is kept to a minimum and the placebo group will be re-assigned to active treatment after Week 16 (primary analysis time point). The blinding is maintained beyond Week 16 so as to ensure reliable efficacy and safety assessments. The regular assessments of disease activity ensures that patients who are experiencing worsening of disease in any of the treatment groups can exit the study upon their own wish or based on the advice of the investigator at any time. Long-term treatment data up to 52 weeks are being generated to explore secukinumab's long-term efficacy and safety in this population.

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

The dosing regimens in this study rely upon dose-efficacy relationships observed in a proof of concept (PoC) trial (CAIN457A2206) and two phase 3 trials (CAIN457F2306, CAIN457F2312) in PsA, as described below. The PoC trial in PsA (CAIN457A2206) suggested that after two i.v. secukinumab doses of 10 mg/kg given 3 weeks apart, secukinumab demonstrated high efficacy, achieving an ACR20 response at Week 6 in 62% of the TNF-naïve patients on secukinumab vs. 20% on placebo, and was well-tolerated (McInnes et al 2013). The phase 3 trials in PsA, CAIN457F2306 assessed the efficacy of both 75 mg and 150 mg s.c. maintenance doses (every 4 weeks) after loading regimens consisting of 3 i.v. doses of 10 mg/kg given at BL, Weeks 2 and 4, and CAIN457F2312 assessed the efficacy of 75 mg, 150 mg and 300 mg s.c. maintenance doses (every 4 weeks) after loading regimens consisting of s.c. doses of 75 mg, 150 mg or 300 mg given at BL, Weeks 1, 2, and 3. Given the similarity of the ACR20 response seen at the Week 24 primary analysis time point for the

150 mg dose in each of these studies, regardless of whether the loading dosing was i.v. (CAIN457F2306: 50.0% for 150 mg vs 17.3% for placebo) or s.c. (CAIN457F2312: 51.0% for 150 mg vs 15.3% for placebo), 150 mg is a sufficient dose to provide clinically and statistically significant efficacy, whereas higher loading doses of secukinumab do not appear to confer a greater response on the primary efficacy variable of ACR20 at Week 24. In Study CAIN457F2312, PASI75 and PASI90 response was assessed in the subgroup of patients who had ≥ 3% skin involvement with psoriasis at baseline. For both PASI75 and PASI90 response rates, the difference to placebo at Week 24 was statistically significant for the secukinumab 150 mg and 300 mg doses (PASI75: 48.3%, $p = 0.0006$ and 63.4%, $p < 0.0001$; PASI90: 32.8%, $p = 0.0029$ and 48.8%, $p = 0.0002$, respectively). The percentage of responders increased as secukinumab dose increased, with the secukinumab 300 mg dose demonstrating a meaningful improvement over the secukinumab 150 mg dose (treatment differences between secukinumab 300 mg and 150 mg for PASI75 and PASI90 were 15.1% and 16.0%, respectively). Of note, the 75 mg s.c. loading (once weekly) followed by maintenance (once monthly) tested in CAIN457F2312 achieved a statistically significant but clinically lower effect size in ACR20 response of 29.3% and did not achieve statistically significant improvements in any of the efficacy variables tested in a pre-defined testing hierarchy, including PASI75, PASI90 DAS28 CRP, SF36 PCS, HAQ-DI©, ACR50, dactylitis and enthesitis.

This study is evaluating secukinumab 300 mg and 150 mg s.c. doses for the treatment of adults with active PsA and a baseline psoriatic skin lesions of PASI 1 and higher . As the phase 3 program suggested that patients with concomitant skin lesions may have more pronounced clinical benefits with 300 mg, all the placebo patients will receive secukinumab 300 mg after the completion of placebo controlled period (Week 16). The non-responders in Group 2 (150 mg patients) will receive secukinumab 300 mg after the completion of Week 16 as well as at every clinical visit until the completion of the study (Weeks 20, 24, 28, 32, 36, 40, 44 and 48) based on their responder status.

Also in order to minimize the patient's exposure to placebo, this study will utilize a 2:2:1 randomization that only 1 out 5 patients will receive placebo for a duration of 16 weeks where the meaningful clinical differentiation is observed in the phase 3 FUTURE studies.

In summary, the secukinumab regimen in this study is based on data suggesting optimal efficacy in PsA and optimal safety and efficacy in the treatment of skin disease in patients with psoriasis.

3.4 Rationale for choice of comparator

A placebo arm is included in this study up to the primary analysis time point at Week 16. Due to the nature of the disease and the outcome measures used (ACR criteria) a placebo arm is necessary to obtain reliable efficacy measurements. The continuation of the placebo group up to the primary analysis time point at Week 16 can be supported from an ethical standpoint. Moreover the inclusion of a placebo group is in accordance with health authority guidelines, including (FDA 1999/EMA 2009). The parallel-group placebo controlled design used in this study is aligned with Phase III trials of other biologics in this disease area and is in accordance with international guidelines. The treatment duration of the placebo group is kept to a minimum and the placebo group will be re-assigned to active treatment at the end of

Week 16. The regular assessment of disease activity ensures that patients who are experiencing worsening of disease in any of the treatment groups can exit the study upon their own wish or based on the advice of the investigator at any time.

3.5 Purpose and timing of interim analyses/design adaptations

The database of this study will be locked twice, first after the end of **Treatment Period 1** (Week 16) and again after the end of **Treatment Period 2** (Week 52). Data analyses will follow each database lock. The main analysis (or test) for the primary objective will be done at Week 16. As Week 16 is the primary analysis time point, no adjustment to the significance level of 0.05 will be made.

3.6 Risks and benefits

Secukinumab has shown confirmed efficacy in several inflammatory diseases and approved by the EMA and FDA for the treatment of active PsA and AS in adult patients. The safety profile of secukinumab is primarily based on the aggregate safety data from 10 large completed phase II/III psoriasis trials. The evaluation of safety data from completed PsA trials did not show additional safety concerns.

Secukinumab was generally safe and well-tolerated. The most frequently reported adverse events (AE) are infections, especially upper respiratory tract with secukinumab relative to placebo. There was an increase in mucosal or cutaneous candidiasis with secukinumab compared to placebo, but the cases were generally mild or moderate in severity, non-serious, and responsive to standard treatment.

There was a small increase in mild neutropenia cases with secukinumab compared to placebo. Common Toxicity Criteria (CTC) AE grade 3 neutropenia (<1.0-0.5×10^9/L) was uncommonly observed with secukinumab, most were transient and reversible without a temporal relationship to serious infections.

Hypersensitivity reactions include urticarial and rare event of anaphylactic reaction to secukinumab were also observed in clinical studies.

Taking into account the individual risks as outlined above, the expected risk profile of secukinumab from a mechanism of action perspective is anticipated to be similar or improved compared to the approved inflammatory cytokine-targeting therapies. The risk to patients in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring and extensive guidance to the investigators, provided in the current version of the IB. The completed FUTURE 1 and 2 trials confirmed the significant clinical benefits to secukinumab treatment in PsA patients observed as early as 1-3 weeks in all PsA related joint, skin and other symptoms such as dactylitis and enthesitis.

From the standpoint of the overall risk-benefit assessment, current trial with secukinumab is justified.

[redacted]

4 Population

The study population will be comprised of the following patients who have passed screening assessments, comply with eligibility criteria and have provided written consent:

Male and female patients aged at minimum 18 at time of consent, with active PsA fulfilling the CASPAR criteria (described in Appendix 2). Patients must have symptoms for at least 6 months with moderate to severe PsA and must have ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 at baseline (dactylitis of a digit counts as one joint each).

Patients must have a target psoriatic skin lesion with a PASI score of 1 or greater at the time of screening.

A total of approximately 250 patients will be randomized in approximately 65 rheumatology/dermatology centers in the United States. A screening failure rate of approximately 30% and post-randomization loss to follow-up rate of 10% is anticipated. Patients who drop out after they have been randomized will not be replaced.

4.1 Inclusion criteria

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

1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed
2. Male or non-pregnant, non-lactating female patients at least 18 years of age
3. Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have had at Baseline ≥ 3 tender joints out of 78 and ≥ 3 swollen joints out of 76 (dactylitis of a digit counts as one joint each)
4. A target psoriatic skin lesion and a PASI score of 1 or greater
5. RF and/or Anti-cyclic citrullinated peptide (anti-CCP) antibodies negative at screening.
6. Patients who are regularly taking NSAIDs as part of their PsA therapy are required to be on a stable dose for at least 2 weeks before study randomization and should remain on a stable dose up to Week 16
7. Patients taking corticosteroids should be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization and must remain on a stable dose up to Week 16
8. Patients taking MTX (≤ 25 mg/week) are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization and must remain on a stable dose up to study completion
9. Patients on MTX must be on folic acid supplementation at randomization
10. Patients who are on a DMARD other than MTX must discontinue the DMARD 4 weeks prior to randomization visit except for leflunomide, which should be discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed.

[redacted]

4.2 Exclusion criteria

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

1. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician
2. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor
3. Use of any investigational drug and/or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug, whichever was longer
4. Ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, ultraviolet therapy) at randomization. The following wash out periods need to be observed:
   a. Oral or topical retinoids 4 weeks
   b. Photochemotherapy (e.g. Psoralen Plus Ultraviolet Light Therapy (PUVA)) 4 weeks
   c. Phototherapy (UVA or UVB) 2 weeks
   d. Topical skin treatments (except in face, eyes, scalp and genital area during screening, only corticosteroids with mild to moderate potency) 2 weeks
5. History of hypersensitivity to the study drug or its excipient or to drugs of similar chemical classes.
6. Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization
7. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization
8. Patients who ever received biologic immunomodulating agents including those targeting TNFα, IL-6 and IL-12/23 investigational or approved
9. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., alemtuzumab, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
10. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test
11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective contraception during the entire study or longer if required by locally approved prescribing information. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

[redacted]

- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that subject
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

- NOTE: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea as defined by Central Lab FSH and/or estradiol levels

12. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy
13. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy
14. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure [New York Heart Association status of class III or IV], uncontrolled diabetes
15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. The investigator should be guided by the following criteria:
    a. Any single parameter should not exceed 2 × upper limit of normal (ULN). A single parameter elevated up to and including 2 × ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out lab error
    b. If the total bilirubin concentration is increased above 2 × ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 µmol/L)
16. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6µmol/L)
17. Screening total White Blood Cells (WBC) count <3,000/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL (85g/L)
18. Active systemic infections during the last two weeks (exception: common cold) prior to randomization
19. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive Purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an

[redacted]

induration of ≥ 5mm or according to local practice/guidelines) or a positive QuantiFERON tuberculosis (TB)-Gold test as indicated in the assessment schedule. Patients with a positive test may participate in the study if further work-up (according to local practice/guidelines) established conclusively that the subject had no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated

20. Known infection with human immunodeficiency virus, hepatitis B or hepatitis C at screening or randomization
21. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)
22. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial
23. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
24. Any medical or psychiatric condition which, in the investigator's opinion, precludes the participant from adhering to the protocol or completing the study per protocol
25. Donation or loss of 400 mL or more of blood within 8 weeks before randomization
26. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization
27. Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Novartis will supply the following study treatments:

- **Investigational Treatment:**
  Secukinumab 150 mg provided in 1.0 mL in PFS for s.c. injection.
- **Reference Therapies:**
  Secukinumab **placebo** provided in 1.0 mL PFS for s.c. injection.

NOTE: The PFS are packed in double blinded fashion for the entire duration of the study. The study medication will be labeled as follows:

- All double blind secukinumab and placebo PFS will be labeled as AIN457 150mg/1.0ml/Placebo. Patients will be provided with detailed instructions and guidance on how to self-administer the s.c. injection using the PFS and following the Instructions for Use (IFU). The investigational drug will be administered by the

subject into the appropriate injection site of the body under the supervision of the site staff at each visit.

For detailed instructions for storage of the study treatments, please refer to Section 5.5.3.1 and the pharmacist manual.

5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

5.2 Treatment groups

At the Baseline Visit, patients will be assigned via Interactive Response Technology (IRT) in a 2:2:1 ratio to one of the three treatment groups (secukinumab 300 mg s.c., secukinumab 150 mg s.c. or placebo s.c.).

Treatment Period 1

- **Group 1- Secukinumab 300 mg**: secukinumab 300 mg (two s.c. injections of the 150 mg dose) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.
- **Group 2- Secukinumab 150 mg**: secukinumab 150 mg (one s.c. injection of the 150 mg dose and one s.c. injection of placebo) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.
- **Group 3- Placebo**: placebo (two s.c. injection of 150 mg secukinumab placebo per dose) once per week for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.

Treatment Period 2

- Patients receiving secukinumab 300 mg (**Group 1**) will continue to receive the same dose up to Week 48.
- At Weeks 16, 28 and 40 patients on secukinumab 150 mg (**Group 2**) will be classified as responders (≥ 20% improvement from BL in both tender and swollen joint counts) or non-responders.
  - At Weeks 16, 28 and 40 patients on secukinumab 150 mg (Group 2) who are responders will continue to receive secukinumab 150 mg (1.0 mL) plus placebo (1.0 mL) every 4 weeks until next evaluation of responder status at Weeks 28 or 40.
  - Patients who did not meet the responder criteria at Week 16, 28 or 40 will start receiving secukinumab 300 mg s.c. every 4 weeks and will continue this dose up to Week 48.
- Patients on placebo (**Group 3**) regardless of their responder status will start receiving secukinumab 300 mg s.c. every 4 weeks from Week 16 up to Week 48.

Patients will self-administer all secukinumab and placebo doses at the study site up to Week 48. After they have received training by the site on how to self-administer their secukinumab and placebo doses.

[redacted]

5.3 Treatment assignment and randomization

At Visit 2/Baseline, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment groups in a ratio of 2:2:1 (secukinumab 300mg: secukinumab 150mg: placebo). The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment group in the system and will specify a unique medication number for the first package of investigational treatment to be dispensed to the subject. The randomization number will not be communicated to any of the site staff.

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

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

5.4 Treatment blinding

Patients, investigators/site staff, persons performing assessments, and Novartis study personnel will remain blinded to individual treatment assignment from the time of randomization until the final database lock using the following methods:

1. Randomization data will be kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:
   - Specific vendors whose role in trial conduct requires their unblinding (e.g., IRT)
   - Drug Supply Management (DSM);
2. The identity of secukinumab and placebo prefilled syringes (PFS) will be concealed by identical packaging, labeling, schedule of administration, and appearance.

As the primary analysis time point is Week 16, there will be a database lock after all patients have completed the Week 16 visit and data are clean and complete. At that time, only the statistician and programmer(s) from the designated CRO will be unblinded in order to perform the analysis. Results from the analyses of all data through Week 16, will be reported. For publication purposes, summary results from the Week 16 primary analysis time point may be shared with the health care community, however individual subject-level data will remain blinded until the end of the trial.

Unblinding will only occur in the case of subject emergencies (see Section 5.5.12), at the time of the primary analysis (Week 16) for designated CRO personnel only, and at the conclusion of the study.

[redacted]

A full analysis of all data will be performed when all patients have completed the study.

5.5 Treating the patient

5.5.1 Patient numbering

Each subject is uniquely identified in the study by a combination of his/her center number and subject number. The center number is assigned by Novartis to the investigative site. After the subject has signed the ICF, the investigator or his/her staff will contact the IRT and provide the requested identifying information for the subject. At each site, the first subject is assigned subject number 1, and subsequent patients are assigned consecutive numbers (e.g. the second subject is assigned subject number 2; the third subject is assigned subject number 3). Once assigned to a subject, a subject number will not be reused. If the subject fails to be randomized for any reason, the IRT must be notified within 2 days and the reason for not being randomized will be entered on the Screening Phase Disposition Form within the eCRF. The appropriate eCRF(s) pages should also be completed.

Patients can only be re-screened once and will receive a new subject number after they have been re-consented. Patients who are mis-randomized cannot be re-screened.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment (active treatment or placebo) in packaging of identical appearance.

The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of this label, which corresponds to placebo or active treatment. Investigator staff will identify the investigational treatment packages to dispense to the subject by contacting the IRT and obtaining the medication numbers. Immediately before dispensing the package to the subject, the investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

5.5.3 Handling of study treatment

5.5.3.1 Handling of Investigational treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in English and comply with legal requirements in the U.S. They will include storage conditions for the investigational treatment but no information about the patient except for the medication number.

The PFS (150 mg active/placebo) sealed in their outer box must be stored in a locked refrigerator between 2°C and 8°C (36°F and 46°F) and protected from light. They must be

[redacted]

carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused investigational treatment and packaging at the end of the study or at the time of discontinuation of investigational treatment.

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

Destruction of the unused drug should be done according to local requirements and after approval by Novartis clinical team.

5.5.4 Instructions for prescribing and taking study treatment

All study treatment (150 mg secukinumab, or placebo) will be self-administered subcutaneously throughout the study after the study assessments for the visit have been completed. Site staff will administer the injection only to those patients who are not able to self-administer the PFS injection. Detailed instructions on the self-administration of the study treatment will be described in the Instructions For Use (IFU) and provided to each subject.

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

The subject will be instructed by the site staff, utilizing the IFU, on how to self-inject via PFS. Patients will be asked to raise any questions, if they have any, and then to proceed with self-injection. Self-injection will take place under the supervision of a site staff member. At the Week 1 and subsequent visits, patients will be asked to refer to the IFU and to proceed with self-injection of the study drug.

Study treatment will be administered weekly following the BL dose (Weeks 1, 2, 3, & 4) and every 4 weeks thereafter (Week 8 until Week 48)

All dates and times of injections self-administered by the subject during the study must be recorded on the Dosage Administration Record eCRF. Immediately before dispensing the drug package to the subject, the investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

The investigator should promote compliance by instructing the subject to attend the study visits as scheduled and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject should be instructed to contact the investigator if he/she is unable for any reason to attend a study visit as scheduled or if he/she is unable for any reason to take the study treatment as prescribed.

[redacted]

5.5.4.1 Administration

Secukinumab Solution for Subcutaneous Injection (active or placebo, respectively) will be provided in prefilled syringes (PFS).

- Secukinumab (active) 150 mg/mL solution in a single-use Sensoready® pen or placebo

Single syringes will be packed in individual boxes. The boxes containing the safety prefilled syringes with study treatment solution should be kept at 2 to 8°C (36°F and 46°F) and protected from light. Prior to administration the boxes containing the safety prefilled syringes with study treatment solution should be allowed to come to room temperature unopened for about 20 minutes before administration. Used safety syringe should be disposed immediately after use in a sharps container.

Patients will be instructed at BL by the site staff on how to self-inject either secukinumab or placebo (blinded) via PFS following the IFU. After the BL visit, the injections will be self-administered into the appropriate site of the body (thighs, arms, abdomen), and each injection should be given at a different injection site. Each new injection should be given at least one inch from the previously used site. If subject chooses the abdomen, 2 inches area around navel should be avoided. Investigational drug should not be injected into areas where the skin is tender, bruised, red, or hard, or where subject has scars or stretch marks. Injection sites should be changed to reduce the risk of reaction.

At study visits when pre-dose blood samples have to be drawn, the study medication will be self-injected only after the blood samples have been taken.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted. Study treatment interruption is also not permitted with the following exceptions:

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

The effect of secukinumab on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. In case a live vaccine has been administered due to a medical urgency, study treatment should be interrupted for 12 weeks. Any study treatment interruption must be recorded on the corresponding Dose Administration Record eCRF page and all assessments should be completed as scheduled.

5.5.6 Rescue medication

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

Rescue medication must not be used before completion of Week 16 assessments.

[redacted]

Changes in NSAIDs concomitant therapy is permitted after Week 16 assessments per investigator's clinical judgment. Any use of rescue medication must be recorded on the corresponding Concomitant Medications eCRF.

Please see Section 5.5.7 for additional details.

5.5.7 Concomitant treatment

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

Guidelines for the use of specific medications are provided below:

Methotrexate (MTX)

Patients taking MTX (up to 25 mg/week) must be on a stable dose for at least 4 weeks before randomization and maintained stable throughout the duration of the study.

Folic acid

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

Leflunomide wash-out with cholestyramine

In case of leflunomide treatment, a wash-out of 8 weeks has to be performed.

However, another wash-out procedure might be considered. Cholestyramine could be given orally to wash-out the leflunomide at a dose of 8 g t.i.d. Cholestyramine reduced plasma levels of the active leflunomide metabolite by approximately 40 % in 24 hours and by 49% to 65% in 48 hours in three healthy volunteers. The administration of cholestyramine is recommended in patients who require a drug elimination procedure. If a subject receives 8 g t.i.d. for 11 days, the subject could be safely randomized 4 weeks after the beginning of the 11-day treatment period.

Systemic corticosteroids

Treatment with systemic corticosteroids is permitted up to a maximum daily dosage of 10 mg prednisone equivalent and the dose is stable within the 2 weeks preceding randomization. The subject should remain on a stable dose until Week 16.

Corticosteroid dose reductions below 10 mg prednisone equivalent are permitted after Week 16, although the corticosteroid dose should not be reduced more than 1 mg prednisone equivalent every 4 weeks. Any change in the dose of systemic corticosteroids during the trial must be recorded on the corresponding eCRF page.

Intra-articular corticosteroids are not permitted within the 4 weeks preceding randomization and up to Week 16. After Week 16, no more than one joint per 24-week period may be injected. No single injection should exceed 40 mg of triamcinolone (or equivalent) and the

[redacted]

total dose of intra-articular corticosteroid may not exceed 80 mg of triamcinolone (or equivalent) during the study.

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

Patients on regular use of NSAIDs, low strength opioids, or acetaminophen PRN should be on stable dose for at least 2 weeks before randomization to allow inclusion. They should remain on a stable dose during the study up to Week 16; however, they have to refrain from any intake at least 1 day before a visit with disease activity assessments.

After the Week 16 assessments are completed, a change in the NSAIDs, low strength opioids, or acetaminophen treatment regimen is permitted

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

5.5.8 Prohibited treatment

Patients who received any biologics such as etanercept, infliximab, adalimumab, golimumab, certolizumab, ustekinumab, cocilizumab, abatacept or rituximab before this study are not allowed to participate in this trial.

Use of the treatments displayed in Table 5-1 below is **NOT** allowed during the study for any indication unless otherwise specified; wash-out periods for these treatments are provided in Table 5-1. If the use of any of these treatments is required, then the subject must not be randomized into the study.

[redacted]

Table 5-1 Prohibited medication

Prohibited treatments	**Washout period (before randomization)**
Conventional DMARDs (except MTX) including [redacted]	4 weeks
Leflunomide	8 weeks
Leflunomide with cholestyramine washout	4 weeks
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Unstable dose of NSAIDs (including selective COX-2 inhibitors)	2 weeks
Analgesics other than NSAIDs, paracetamol/acetaminophen, and low strength opioids PRN	2 weeks
Systemic corticosteroids > 10 mg prednisone equivalent	2 weeks
Unstable dose of systemic corticosteroids ≤ 10 mg prednisone equivalent	2 weeks
Intra-articular corticosteroids injections	4 weeks
Intramuscular or intravenous corticosteroid treatment	4 weeks
Live vaccinations	6 weeks
Oral or topical retinoids	4 weeks
Photochemotherapy (e.g. PUVA)	4 weeks
Phototherapy (UVA or UVB)	2 weeks
Topical skin treatments (except in face, eyes, scalp and genital area during screening, only corticosteroids with mild to moderate potency)	2 weeks

[redacted]

5.5.9 Discontinuation of study treatment

Study treatment must be discontinued if the investigator determines that continuation of study treatment would result in a significant safety risk for a subject. The following circumstances **require** study treatment discontinuation:

- Withdrawal of informed consent
- Emergence of the following adverse events:
  a. Any severe or serious adverse event that is not compatible with administration of study medication, including adverse events that require treatment with an unacceptable co-medication
  b. Onset of lymphoproliferative disease or any malignancy except for treated basal cell carcinoma, treated actinic keratoses, treated in situ carcinoma of the cervix or non-invasive malignant colon polyps which are being or have been removed
  c. Life-threatening infection
- Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the subject at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in (Appendix 1).
- Pregnancy
- Use of any biologic immunomodulating agent except secukinumab (please refer to section 5.5.8 for the other prohibited medications. Any protocol deviation that results in a significant risk to the subject's safety

In addition to these requirements for study treatment discontinuation, the investigator should discontinue study treatment for a given subject if there is a lack of improvement or worsening of their symptoms, or if on balance, he/she thinks that continuation would be detrimental to the subject's well-being.

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

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

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

5.5.10 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore, and does not want any further visits or assessments, and does not want any further study-related contacts, and does not allow analysis of already obtained biologic material.

[redacted]

If premature withdrawal occurs for any reason, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information on the appropriate study completion eCRF.

Patients who prematurely discontinue or withdraw during a specific treatment period should return for a final visit (see Table 6-1). The final visit should be scheduled approximately four weeks after the last study treatment, and should be performed before any new treatment is initiated.

Patients who are prematurely withdrawn from the study will not be replaced by newly enrolled patients.

5.5.11 Loss to follow-up

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

5.5.12 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition.

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

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable.

5.5.13 Study completion and post-study treatment

A subject's individual study participation is completed once Visit 19/Week 52 Treatment Period has been completed. Any SAEs that occur in the following 84 days (12 weeks) after the dose of study drug must be reported. The investigator will also follow any AEs for which there is no outcome that can be reported at the final study visit.

The study as a whole will be completed once all randomized patients have completed the study as per the protocol and the clinical database has been locked. Recruitment into the study will be terminated by the sponsor once the targeted number of randomized patients has been met or is foreseen to be met with the patients already in screening. Patients who have been screened and have a screening visit recorded in the IRT system at the time that the planned

enrollment number is met will be allowed to enter the trial and to be randomized if they are eligible.

Upon completion of their study participation, patients will return to individual treatment, as determined by their treating physician.

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

5.5.14 Early study termination

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrollment). Should this be necessary, the subject should be seen as soon as possible and treated as a prematurely withdrawn as described in Section 5.5.9 The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing Institutional Review Board/Independent Ethics Committee (IRBs/ECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments, indicated with an "X" at the visits they are performed from screening to Week 52.

Patients should be seen for all visits on the designated day, or as closely as possible to the original planned visit schedule (recommended visit windows are in Table 6-1). Every effort should be made to respect the time frame for the Week 16 visit.

- For visits scheduled through Week 4, the study treatment should not be administered within less than 7 days after the previous administration
- For visits scheduled after Week 4, the study treatment should not be administered within less than 14 days after the previous administration

Patient Screening

Screening will be flexible in duration based on the time required to wash out prior anti-rheumatic medications and have a duration of up to 8 weeks before randomization. During which time the subject will sign the informed consent form (ICF), be evaluated for eligibility, and allowed sufficient time for medication washout, if required (see Table 5-1), in addition to other assessments indicated in Table 6-1.

If patients do not have a chest X-ray available within 3 months of screening, the X-ray should be performed only after it is certain the subject meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation.

Patients evaluated at visit 1 and 2 for Inclusion/Exclusion criteria should not be screen failed on the basis of a medication requiring washout, unless the subject will be unable to complete the washout in the appropriate time frame before randomization.

[redacted]

Premature Discontinuation

For patients who discontinue study treatment prematurely for any reason before the end of **Treatment Period 1**, (Visit 10/Week 16 EOT1) must be performed approximately four weeks after the last dose of study treatment (secukinumab 300 mg, secukinumab 150 mg or placebo). Patients should also be contacted via telephone, 84 days (12 weeks) after last dose of study drug, to inquire about any AE/SAEs that occurred during this period.

For patients who discontinue study treatment prematurely for any reason before the end of **Treatment Period 2**, (Visit 19/ Last visit EOT2) must be performed approximately four weeks after the last dose of study treatment (300 mg or 150 mg s.c. secukinumab). Patients should also be contacted via telephone, 84 days (12 weeks) after last dose of study drug, to inquire about any AE/SAEs that occurred during this period.

If patients refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the reason.

At a minimum, patients will be contacted for safety evaluations during the 84 days (12 weeks) following the last study visit or following the last administration of study treatment (whichever is later), including a final contact at the 84-day point. Documentation of attempts to contact the subject should be recorded in the source documentation.

AE/SAE information obtained as a result of these calls must be recorded in the eCRF.

Unscheduled visits

Patients may be seen at any time for an unscheduled visit, e.g., if they experience deterioration or AEs that in the opinion of the investigator/qualified site staff need intervention or repeat laboratory testing. The assessment(s) performed at an unscheduled visit must include at minimum: an assessment of concomitant medication and procedures/significant non-drug therapies, vital signs, and an AE/SAE assessment. Any additional assessments performed are at the investigator/qualified site staff's discretion. During an unscheduled visit, study treatment will not be administered.

[redacted]

Table 6-1 Assessment schedule

Period	SCR[1]		Treatment Period 1								Treatment Period 2										Unscheduled Visit
Week	-8 to BL		BL	1	2	3	4	8	12	16/EOT	20	24	28	32	36	40	44	48	52/EOT	Day 84 Safety Follow-up[4]	
Visit No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19		
Visit Window (days)[2]				+/-2	+/-2	+/-2	+/-2	+/-2	+/-2	+/-2	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7		
Assessments																					
Obtain informed consent	X																				
Inclusion/exclusion criteria	X	X	X																		
Demographics	X																				
Psoriasis/PsA medical history / previous therapies	X																				
Relevant medical history/current medical conditions	X																				
Washout evaluation/instruction	X																				
PsA CASPAR criteria		X																			
Smoking and alcohol history			X																		
Cardiovascular medical history	X																				
Physical Exam[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Height		X																			

[redacted]

Weight		X	X							X									X		
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Chest X-ray[5]		X																			
ECG		X																			
Prior/Concomitant medication/ non-drug therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Randomization via IRT			X																		
Administration of sc study treatment via PFS at study site			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse Events/SAEs[3] (incl. injection site reaction & occurrence of infections)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QuantiFERON TB-Gold test		X																			
Hematology, blood chemistry [6]		X	X						X	X			X			X			X		
Serum pregnancy test		X																			
Urinalysis/Urine pregnancy test [7]			X				X		X	X		X		X		X			X		
Anti-CCP	X																				
Rheumatoid factor (RF)	X																				
High sensitivity C-Reactive protein (hsCRP)		X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Erythrocyte Sedimentation Rate (ESR) [7]		X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Tender and swollen joint		X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		

[redacted]

counts (TJC78, SJC76)																					
Enthesitis evaluation[8]			X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Dactylitis evaluation			X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Physician's global assessment of disease activity (VAS)			X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
PASI			X	X			X	X	X	X		X		X		X			X		
IGA mod 2011			X	X			X	X	X	X		X		X		X			X		
VAS physician's assessment of nail disease			X				X	X	X	X		X		X		X			X		
Health Assessment Questionnaire (HAQ-DI)			X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Patient's assessment of PsA pain (VAS)			X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Patient's global assessment of disease activity (VAS)			X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Patient's global assessment of psoriasis and arthritis disease activity(VAS)			X	X			X	X	X	X		X		X		X			X		
SF-12			X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		

Responder Status Assessment[9]										X	X	X	X	X	X	X	X	X	X		
[redacted]																					
Treatment period 1 completion form										X											
Treatment period 2 completion form																			X		
[redacted]																					

[1] If washout period is ≤ 4 weeks, visit 1 & visit 2 can be performed the same day

[2] Patients who discontinued prematurely or withdrawn during a specific treatment period should return for a final visit. The final visit should be scheduled approximately four (4) weeks after the last study treatment, and should be performed before any new treatment is initiated

[3] AEs/SAEs occurring after informed consent has been obtained must be reported. Patients who **discontinued prematurely** should be contacted **via telephone** to collect AE/SAEs information. Any AE/SAEs that occur in the following 84 days (12 weeks) after last dose of study drug must be reported.

[4] These assessments are source documented only and will not be entered into the eCRF

[5] Not necessary if done within past 3 months. If not, should be scheduled only after patient has met inclusion/exclusion criteria

[6] Fasting sample

[7] Tests performed locally using kits supplied by central lab

[redacted]

[9] Those patients on secukinumab 150 mg who are non-responders at Week 16, 28, or 40 will start receiving secukinumab 300 mg s.c. every 4 weeks up to Week 48.

[redacted]

6.1 Information to be collected on screening failures

All patients who sign informed consent but discontinue prior to randomization at Visit 3 are considered screening failures. The IRT must be notified about the discontinuation, and the primary reason for the screen failure should be entered in the Screening Phase Disposition eCRF.

In addition, only the following eCRFs should be completed: Demography eCRF, Informed Consent eCRF, Inclusion/Exclusion eCRF, and the adverse event (AE) eCRF should be completed for any Serious Adverse Events (SAEs) that occurred during the screening period. Adverse events that are not serious will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

All baseline assessments should be performed prior to the first study treatment administration.

6.2.1 Demographics

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

- date of birth, subject initials, gender, race, and child-bearing potential (for females only).

6.2.2 PsA/Psoriasis history/ Prior psoriasis therapies

Disease history will be collected at the screening visit. The information to be collected and entered in the eCRF includes the following:

- date of first diagnosis of plaque psoriasis (by a physician)
- presence of psoriatic arthritis and the date of first diagnosis (by a physician)
- disease duration (if different from time since diagnosis)
- previous PsA/psoriasis treatments (including previous use of biologic therapies, as well as phototherapy and/or photo chemotherapy) and the reason for discontinuation of each therapy

6.2.3 Smoking history

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

6.2.4 Co-morbidities-Cardiovascular history

Any information pertaining to cardiovascular medical history assessed prior to signing informed consent should be reported on the Cardiovascular History eCRF.

6.2.5 Relevant medical history / Current medical conditions

Whenever possible, diagnoses and not symptoms will be recorded.

[redacted]

Relevant medical history/current medical conditions, not including psoriasis or psoriatic arthritis, will be recorded on the Medical History eCRF.

Relevant medical history/current medical conditions will include data up to six months prior to signing of the informed consent. Whenever possible, diagnoses (and not symptoms) will be recorded.

Significant findings that are observed after the subject has provided informed consent, and that meet the definition of an AE, must be recorded on the Adverse Event eCRF.

Investigators will have the discretion to record abnormal test findings on the Medical History eCRF when in their judgment, the test abnormality occurred prior to the informed consent signature.

6.2.6 Prior and concomitant medications

Concomitant medications and prior medications taken over the six months preceding study enrollment will be captured at the Screening visit, and updated at Visit 3 (Randomization).

6.2.7 Chest X-ray

A chest X-ray, CT scan, or MRI obtained within 3 months prior to randomization will be used to determine eligibility. If patients do not have a chest X-ray, CT scan, or MRI available within 3 months prior to randomization, a chest X-ray only must be done after it is fairly certain the subject meets the other inclusion/exclusion criteria in order to minimize unnecessary exposure to X-ray radiation for patients.

If the chest X-ray, CT scan, or MRI evaluated by a qualified physician shows evidence of ongoing infection or malignancy and the subject was not treated subsequent to the X-ray (CT scan or MRI), the subject will not be eligible to enter the study.

6.2.8 Determination of tuberculosis status

Determination of tuberculosis (TB) status will be required before administration of study treatment. TB status must be determined by medical history, signs, symptoms, and TB testing (QuantiFERON-TB Gold assay). Any significant findings will be recorded in the appropriate eCRF(s), as necessary.

If the QuantiFERON-TB Gold Assay test is positive or indeterminate, a TB workup should be performed as defined by local guidelines to determine the subject's TB status.

QuantiFERON TB-Gold In-Tube assay

A QuantiFERON® TB-Gold In-Tube assay will be performed to assess the TB status at screening for all patients. This test will only be used to determine subject's eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection (Doherty et al 2008).

This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin vaccination or exposure to other Mycobacteria species.

This test, in contrast to the purified protein derivative (PPD) skin test, is also insensitive to a booster effect since the subject is not exposed to the vaccine. The assay measures the

[redacted]

production of interferon-gamma and presents it relative to a negative and a positive control sample (Manuel and Kumar 2008)

The QuantiFERON®-TB Gold assay test will be supplied by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the Laboratory Manual.

The results of a TB workup for a subject with a positive or indeterminate test must be recorded in the eCRF.

- If the test result is **negative**, the subject may be randomized.
- If the test result is **positive**, the investigator should perform a TB workup for the test result as per local procedures.
- Patients **positive** for latent TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration.
- Patients **positive** for active TB per workup are not eligible for the study.
- Patients **negative** for TB (no signs of latent or active TB) per workup may be randomized to the trial.
- If the test result is **indeterminate**, it is **recommended to repeat the test once**. The investigator may decide to skip the repetition of the test and proceed directly to the workup (however this is not recommended). If a TB workup was conducted prior to screening, results from the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to randomization.
- If the second test is negative, the subject may be randomized.
- If the second test is positive or indeterminate, the investigator should perform a TB workup as per local guidelines. The subject will not be eligible for randomization if: "active tuberculosis is present", or if "latent tuberculosis is present" and is untreated as per local guidelines.

6.3 Treatment exposure and compliance

All doses of secukinumab or placebo administration will be recorded on the Dosage Administration Record eCRF. Compliance will be assessed by Novartis and CRO study personnel using the Dosage Administration Record eCRF, medication numbers, Drug Label Form information, and information collected by IRT.

Compliance is expected to be 100% since all doses of study treatment will be administered **at the site** in the presence of the investigator or site staff, unless temporary interruption is needed for safety reasons as described in Section 5.5.5.

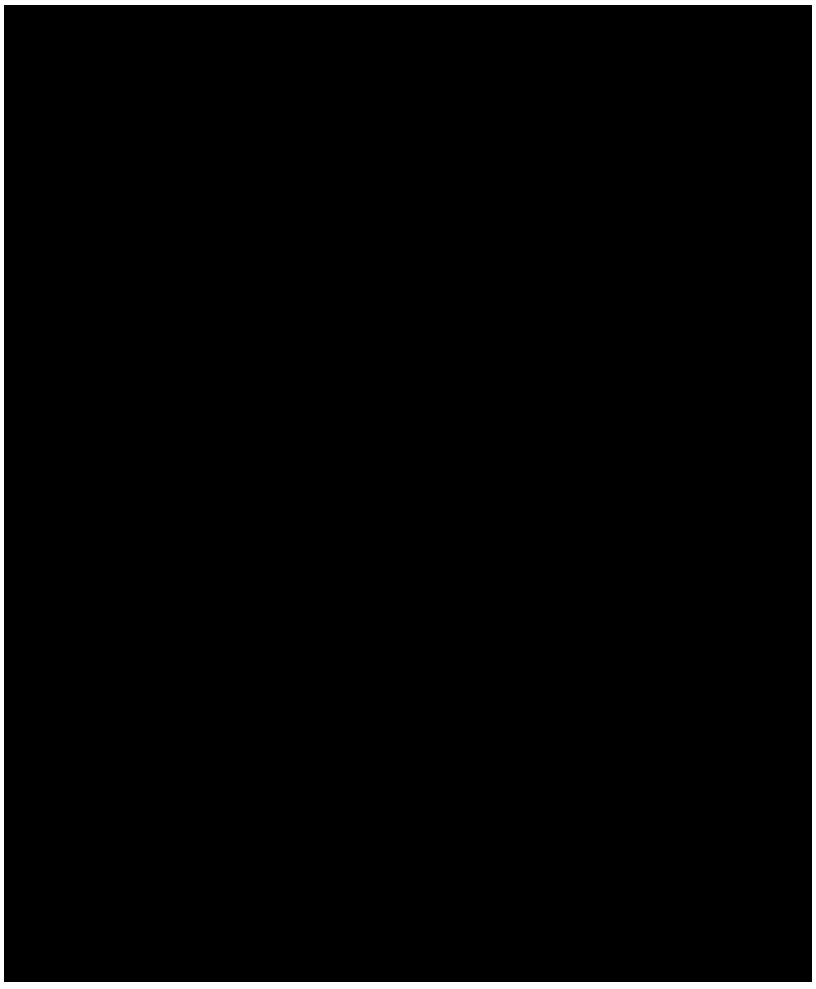
6.4 Efficacy

The primary efficacy variable is ACR20 response (yes, no). The primary analysis time point will be at Week 16.

The secondary efficacy variables are the following:

[redacted]

1. Dactylitis (yes, no)
2. Enthesitis (yes, no)
3. ACR50 response (yes, no)
4. ACR70 response (yes, no)
5. Minimal Disease Activity (yes, no)
6. PASI75 response (yes, no)
7. PASI90 response (yes, no)
8. PASI100 response (yes, no)
9. Change from baseline in DAS28-CRP
10. Change from baseline in PASDAS
11. Change from baseline in SF12
12. Change from baseline in HAQ-DI



6.4.1 American College of Rheumatology (ACR) response

The ACR response (Appendix 4) will be used to determine efficacy (Felson 1995)-*A subject is defined as e.g. an ACR20 responder if, and only if, the following three conditions hold:

- they have a ≥ 20% improvement in the number of tender joints (based on 78 joints)
- they have a ≥ 20% improvement in the number of swollen joints (based on 76 joints)
- they have a ≥ 20% improvement in three of the following five domains:
  - Patient's global assessment of disease activity (measured on a VAS scale, 0-100)
  - Physician's global assessment of disease activity (measured on a VAS scale, 0-100)
  - Patient's assessment of PsA pain (measured on a VAS scale, 0-100)
  - Health Assessment Questionnaire (HAQ©) score
  - Acute phase reactant (hsCRP or ESR)

ACR50 = 50 % improvement in at least 3 of the 5 domains and 50 % improvement in the swollen and tender joint count.

ACR70 = 70 % improvement in at least 3 of the 5 domains and 70 % improvement in the swollen and tender joint count.

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

6.4.2 Tender 78 joint count and swollen 76 joint count

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

The 78 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 2 first carpometacarpal, 10 metacarpophalangeal, 10 proximal interphalangeal, 8 distal interphalangeal joints of the hands, the 2 hip, 2 knee, 2 talo-tibial, 2 mid-tarsal, 10 metatarsophalangeal, 10 proximal interphalangeal, and 8 distal interphalangeal joints of the feet. All of these except for the hips are assessed for swelling. Joint tenderness and swelling are to be graded present (1) or absent (0). Synovial fluid and/or soft tissue swelling but not bony overgrowth represents a positive result for swollen joint count. Dactylitis of a digit in the foot or hand counts as one tender and swollen joint.

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

6.4.3 Patient Reported Outcomes (PRO)/QoL Assessments

Patients should complete all assessments prior to any investigator evaluations.

- Patient's Assessment of PsA pain intensity
- Patient's global assessment of disease activity (VAS)
- Patient's global assessment of psoriasis and arthritis disease activity (VAS)

The impact of PsA on various aspects of patients' health-related quality of life (HRQoL) will be assessed using the following validated instruments:

[redacted]

- Health Assessment Questionnaire (HAQ-DI)
- SF-12

[redacted]

All questionnaires will be completed at the defined visits/ time points listed in Table 6-1, and prior to the subject seeing the investigator for any clinical assessment or evaluation. The subject should be given sufficient instruction, space, time and privacy to complete the questionnaires. The study coordinator should check the questionnaires for completeness and encourage the subject to complete any missing responses. Completed questionnaires should be reviewed and assessed by the investigator before the clinical examination, for responses which may indicate potential AEs or SAEs. This assessment should be documented in the source records. If AEs or SAEs are confirmed the investigator should record the events as per instructions given in the relevant section of the protocol (see Section 7).

Guidelines for administering the PRO questionnaires can be found in Appendix 10.

6.4.3.1 Patient's assessment of PsA pain intensity

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

6.4.3.2 Patient's global assessment of disease activity

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

6.4.3.3 Health Assessment Questionnaire (HAQ-DI)

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

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

[redacted]

6.4.3.4 Medical Outcome Short Form Health Survey (SF-12) Version 12

The SF-12v2® Health Survey is a shorter version of the SF-36v2® Health Survey that uses just 12 questions to measure functional health and well-being from the patient's point of view.

Taking only two to three minutes to complete, the SF-12v2® is a practical, reliable and valid measure of physical and mental health and is particularly useful in large population health surveys or for applications that combine a generic and disease-specific health survey. The SF-12v2® covers the same eight health domains as the SF-36v2® with one or two questions per domain.

As the survey uses norm-based scoring, comparisons can be made among the other generic health surveys such as SF-36v2 and it can measure outcomes concisely at the population level, and it is a widely used tool for monitoring population health, comparing and analyzing disease burden and predicting medical expenses.

The purpose of the SF-12 in this study is to assess the HRQoL of patients. Given the acute nature of this disease, version 2, with a 1-week recall period, will be used in this study.

6.4.4 Physician's global assessment of disease activity

The physician's global assessment 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 subject.

6.4.5 High Sensitivity C-reactive protein (hsCRP)

Blood for this assessment will be obtained in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment.

Since the results of this test may unblind study personnel, results from the central lab will be provided for screening and baseline only. The hsCRP results from samples collected during the treatment period will be revealed following database lock only.

6.4.6 Erythrocyte sedimentation rate (ESR)

ESR tests MUST be performed locally. Blood for ESR, which is helpful in diagnosing inflammatory diseases and is used to monitor disease activity and response to therapy, will be obtained at scheduled visits as indicated in Table 6-1.

[redacted]

6.4.8 DAS28 and EULAR response

The DAS28 is a measure of disease activity based on Swollen and Tender Joint Counts, ESR or CRP and the Patient Global Assessment. A DAS28 score > 5.1 implies active disease, ≤ 3.2 low disease activity, and < 2.6 remission. EULAR response criteria are based on DAS28 status in combination with DAS28 improvements.

6.4.9 Psoriatic Arthritis Disease Activity Score (PASDAS)

PASDAS is a new composite measure developed to access disease activity in Psoriasis (GRACE Project) (Helliwell 2012). It is calculated by utilizing seven measures; the seven components are: Patient reported measures (excluding mental component summary score (MCS) of the medical outcomes survey Short Form-36 (SF-36-PCS)), skin, peripheral joint counts (Tender and Swollen joint counts), Dactylitis (LDI), [redacted] acute phase response (CRP) and Patient & Physician global VAS scores.

PASDAS = (0.18 x √Physician global VAS)

+ (0.159 x √Patient global VAS)

- (0.253 x √SF36-PCS)

+ (0.101 x LN (Swollen joint count + 1))

+ (0.048 x LN (Tender joint count + 1))

+ (0.23 x LN (Leeds Enthesitis Count + 1))

+ (0.377 LN (Dactylitis count + 1))

+ (0.102 x LN (CRP + 1)) +2)*1.5.

VAS for PASDAS assessment:

Instruct patients to place marks on the lines below to indicate answer to the following questions relating to the past week.

Global Disease Activity: The patient's assessment of PSORIASIS and ARTHRITIS will be performed using 100 mm VAS ranging from "Excellent" to "Poor" after the question

[redacted]

"Considering all the ways PSORIASIS and ARTHRITIS affects you, please indicate with a vertical mark (|) through the horizontal line how well you are doing over the past week".

6.4.10 Minimal disease activity

The proportion of patients achieving minimal disease activity (MDA (Coates 2010) (5 of the 7 following: ≤ 1 tender joint count, ≤ 1 swollen joint count, PASI ≤ 1 or IGA ≤ 1, patient pain VAS ≤ 15, patient global VAS ≤ 20, HAQ-DI ≤ 0.5, tender entheseal points ≤ 1).

6.4.11 Dactylitis Assessments

[redacted]

Presence of dactylitis

If dactylitis is present with any finger or toe, the subject is counted as a subject with dactylitis.

6.4.12 Enthesitis Assessments

Presence of enthesitis:

If enthesitis is present with any of the 18 sites below, the subject is counted as a subject with enthesitis.

- Medial epicondyle humerus (left/right (L/R)
- Lateral epicondyle humerus (L/R)
- Supraspinatus insertion into greater tuberosity of humerus (L/R)
- Greater trochanter (L/R)
- Medial condyle femur (L/R)
- Quadriceps insertion into superior border of patella (L/R)
- Patellar ligament insertion into inferior pole of patella or tibial tubercle (L/R)
- Achilles tendon insertion into calcaneum (L/R)
- Plantar fascia insertion into calcaneum (L/R)

[redacted]

[redacted]

[redacted]

[redacted]

6.4.14 Psoriasis Area and Severity Index (PASI)

The PASI assessment will be conducted for patients in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at BL. The PASI assesses the extent of psoriasis on four body surface areas (head, trunk and upper and lower limbs) and the degree of plaque erythema, scaling and thickness. A PASI score (Fredriksson and Pettersson 1978, Weisman 2003, Gottlieb 2005) will be derived as indicated in Table 6-2.

The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

The neck is assessed as part of the head.

The axillae and groin are assessed as part of the trunk.

The buttocks are assessed as part of the lower limbs.

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

[redacted]

Table 6-2 The PASI scoring system

Body region	Erythema (E)	Thickening (plaque elevation, induration)(I)	Scaling (desquamation) (D)	Area score (based on true area %)(A)*
Head (H)**	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 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 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 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 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 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 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 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.

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

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

where E = erythema, I = induration, S = scaling, and A = area,
H = Head, U = Upper limbs, T = Trunk, and L = Lower limbs

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0. The investigator is only responsible for collecting the components or scoring signs and total regional area. More information is provided in Appendix 6.

[redacted]

6.4.15 Investigator's Global Assessment (IGA mod 2011)

IGA mod 2011 will be conducted for overall psoriatic disease as indicated in Table 6-3 for patients in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at BL. It is recommended that the same evaluator conducts the assessment throughout the study wherever possible.

The IGA mod 2011 rating scale has been developed based on a previous version of the scale used in secukinumab phase II psoriasis studies in collaboration with health authorities in particular the FDA. The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points (see Table 6-3).

The IGA mod 2011 used in this study is static, i.e. it refers exclusively to the subject's disease state at the time of the assessments, and does not attempt a comparison with any of the subject's previous disease states, whether at baseline or at a previous visit.

The IGA mod 2011 score will be recorded in the eCRF at the given visits/time points of Table 6-1.

Table 6-3 The IGA mod 2011 rating scale

Score	Short Description	Detailed Description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present.
1	Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling.
2	Mild	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling.
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling.
4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe / coarse scaling covering almost all or all lesions.

Note: Involvement of nails is not part of the assessment.

Based on this scale, a subject will be considered as IGA 0 or 1 responder if the subject achieves a score of 0 or 1 and improved by at least 2 points on the IGA scale compared to baseline.

[redacted]

[redacted]

[redacted]

6.4.17 Physician's global assessment of fingernail disease severity (VAS)

The physician's assessment of nail disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question *"After you have viewed all the fingernails of a subject, consider all aspects of the subject's fingernails and place a vertical line on the scale giving a global assessment of their fingernails"*.

[redacted]

6.4.19 Appropriateness of efficacy assessments

The efficacy assessments used in this study are the standard assessments used across many psoriatic arthritis trials.

[redacted]

6.5 Safety

Evaluation of all AEs and SAEs including injection site reactions, ECGs, physical examination, vital signs and laboratory assessments, Assessment of anti-secukinumab antibody development (immunogenicity).

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

- Evaluation of AE/ SAE's
- Physical examination
- Vital signs
- Height and weight
- QuantiFERON TB-Gold test or PPD skin test
- Electrocardiogram
- Local tolerability (Injection site reactions)
- Laboratory evaluations (Hematology, Clinical Chemistry, LFTs, Urinalysis)
- Pregnancy and assessment of fertility
- Tolerability of secukinumab

6.5.1 Physical examination

A complete physical examination will be performed by a professionally trained physician or health professional licensed to perform physical examinations and listed on FDA Form 1572, at the scheduled study visits as indicated in Table 6-1.

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

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

6.5.2 Vital signs

Vital signs include BP and pulse rate measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using a validated device with an appropriately sized cuff.

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

Clinically notable vital signs are defined in Appendix 1.

[redacted]

6.5.3 Height and weight

Height and body weight (in indoor clothing but without shoes) will be measured at scheduled study visits as indicated in Table 6-1. If possible, body weight assessments should be performed using the same scale throughout the study. The Body Mass Index will be calculated programmably.

6.5.4 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as indicated in Table 6-1. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents.

Clinically relevant abnormalities should be recorded on the relevant medical history/Current medical conditions eCRF page for the baseline ECG.

Clinically relevant abnormalities noted after the baseline ECG should be reported as AE (see Section 7)

6.5.5 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected listed below (except urinalysis). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. For the identification of clinically notable values, see Appendix 1. All patients with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

6.5.5.1 Hematology

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

6.5.5.2 Clinical chemistry

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

6.5.5.3 Urinalysis

Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments. The urinalysis results for standard parameters such as protein, glucose, blood and WBCs will be recorded in the appropriate eCRF page. Follow-up of abnormal results is left to the discretion of the investigator.

6.5.6 Pregnancy and assessments of fertility

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

A serum β-hCG test will be performed in all women of child bearing potential at Screening Visit 2; and a local urine pregnancy test at the specified visits as indicated in Table 6-1. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the subject must be discontinued from the trial.

6.5.7 Tolerability of secukinumab

Tolerability will be assessed by adverse events, laboratory values and injection site reaction.

6.5.8 Additional parameters

Blood will be obtained at the first screening visit (Visit 1) for anti-CCP antibodies and the Rheumatoid Factor (RF).

6.5.9 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic in PsA. A chest X-ray at screening (or within 3 months prior to screening) is performed to rule out the presence of a pulmonary malignancy or infectious process, in particular tuberculosis. The radiation exposure that results from the chest X-ray safety measurements are estimated to be far below 1 mS. Effective radiation doses under 3 mS (300 mrem), are considered to be minimal risk. Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure reliable safety measures before the treatment with a biologic.

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

7 Safety monitoring

7.1 Adverse events

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

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

[redacted]

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

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

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

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

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- relationship to the study treatment (no/yes)
- duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE)
- action taken regarding study treatment
- All adverse events should be treated appropriately. Treatment may include one or more of the following:
  - no action taken (i.e. further observation only)
  - study treatment temporarily interrupted
  - study treatment permanently discontinued due to this adverse event
  - concomitant medication given
  - non-drug therapy given
  - patient hospitalized/patient's hospitalization prolonged
- outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal or unknown)

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

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

[redacted]

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

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

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

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

[redacted]

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

7.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 84 days after the last dose of study medication, must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 84-day period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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

Information about all SAEs (either initial or follow up information) is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship of each SAE to study treatment, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the subject's source documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to relevant ethics committees in accordance with regulatory requirements.

7.3 Liver safety monitoring

There has been no safety signal for liver toxicity with secukinumab to date in over 6535 patients exposed and from a mechanism of action standpoint there is no effect of blocking IL-17A on the liver. Liver function tests will be obtained at regular intervals but special measures for liver safety monitoring are not planned.

[redacted]

7.4 Pregnancy reporting

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

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

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

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

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

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to US CFR 21Part 11

[redacted]

requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

A CRO working on behalf of Novartis will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. Randomization codes and data about all study drug(s) assigned to the subject will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the IRT database. The database will be sent electronically to Novartis (or a designated CRO). Each occurrence of a code break via IRT will be reported to the clinical team and study monitor. The code break functionality will remain available until study completion or upon request of Novartis.

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

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

PRO questionnaires will be completed by the subject on an electronic tablet, and the data transmitted into the eCRF by investigator site staff.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

A designated Contract Research Organization will perform the statistical analysis.

[redacted]

It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of patients will be available for analysis.

Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

Efficacy, safety, and other data will be summarized. For continuous variables, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum) at each time point and for change from baseline to each time point will be reported by treatment group.

9.1 Analysis sets

The following analysis sets will be used for the statistical reporting and analyses:

Randomized Set: The Randomized Set includes all randomized patients.

Safety Set: The Safety Set includes all patients who received at least one dose of study medication. Patients will be included in the analysis according to treatment received.

Full Analysis Set: The Full Analysis Set comprises all patients to whom study medication has been assigned. Patients inappropriately randomized (e.g., IRT was called in error for randomization of a screen failed subject) will be excluded from this analysis set. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

9.2 Patient demographics and other baseline characteristics

Data will be summarized with respect to demographic and baseline characteristics of all patients, the subgroup of patients with dactylitis at baseline, and the subgroup of patients with enthesitis at baseline, for the Randomized Set and the Full Analysis Set.

9.3 Treatments

The number of patients and the length of time (in days) exposed to each treatment will be summarized for the Safety Set.

Concomitant medications will be summarized by treatment using frequency counts and percentages for the Safety Set.

Any condition entered as medical history or current medical condition at baseline will be coded using the MedDRA dictionary for the Safety Set. They will be summarized by system organ class and preferred term of the MedDRA dictionary.

9.4 Analysis of the primary variable

9.4.1 Variable

The primary efficacy variable is ACR20 response (yes, no). The primary analysis time point will be at Week 16.

[redacted]

9.4.2 Statistical model, hypothesis, and method of analysis

Let π_j denote the probability of an ACR20 response at Week 16 for treatment group j, j = 0, 1, 2, where 0 corresponds to placebo, 1 corresponds to secukinumab 150 mg, and 2 corresponds to secukinumab 300 mg. Accordingly, $\pi_j/(1 - \pi_j)$ is the odds for treatment group j, j = 0, 1, 2.

The following null hypotheses (H_{01} and H_{02}) will be tested against their corresponding alternative hypotheses (H_{A1} and H_{A2}):

H_{01}: $[\pi_1/(1 - \pi_1)]/[\pi_0/(1 - \pi_0)] \leq 1$ versus H_{A1}: $[\pi_1/(1 - \pi_1)]/[\pi_0/(1 - \pi_0)] > 1$

H_{02}: $[\pi_2/(1 - \pi_2)]/[\pi_0/(1 - \pi_0)] \leq 1$ versus H_{A2}: $[\pi_2/(1 - \pi_2)]/[\pi_0/(1 - \pi_0)] > 1$

The primary efficacy variable will be analyzed at each time point using a logistic regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight as explanatory variables (Stokes, Davis, and Koch, 2012). The odds ratios for each dose of secukinumab versus placebo, 95% confidence intervals for the odds ratios, and p-values based on the fitted model will be reported. If the p-value for a dose of secukinumab versus placebo is < 0.05 and the corresponding odds ratio is greater than 1, statistical significance in favor of that dose of secukinumab is shown.

The primary analysis of the primary efficacy variable will be based on the Full Analysis Set.

9.4.3 Handling of missing values/censoring/discontinuations

Patients who discontinued prematurely for any reason will be considered non-responders from the time they discontinued. Patients who do not have the required data to compute ACR response (i.e., tender and swollen joint counts and at least three of the five ACR domains) at baseline and at the specific time point will be classified as non-responders.

9.4.4 Supportive analyses

The primary efficacy variable will also be analyzed at each time point for the Full Analysis Set using the Cochran-Mantel-Haenszel (CMH) test to compare each dose of secukinumab against placebo, adjusting for methotrexate usage at baseline (yes, no) (Stokes, Davis, and Koch, 2012). If the treatment comparison p-value is < 0.05 and the proportion of patients who are ACR20 responders is higher in a secukinumab treatment group compared to the placebo treatment group, statistical significance in favor of that dose of secukinumab is shown. Two 95% confidence intervals for the difference between each dose of secukinumab versus placebo in the proportion of patients who are ACR20 responders will be calculated using the normal approximation to the binomial distribution.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary efficacy variables are the following:

1. Dactylitis (yes, no)

[redacted]

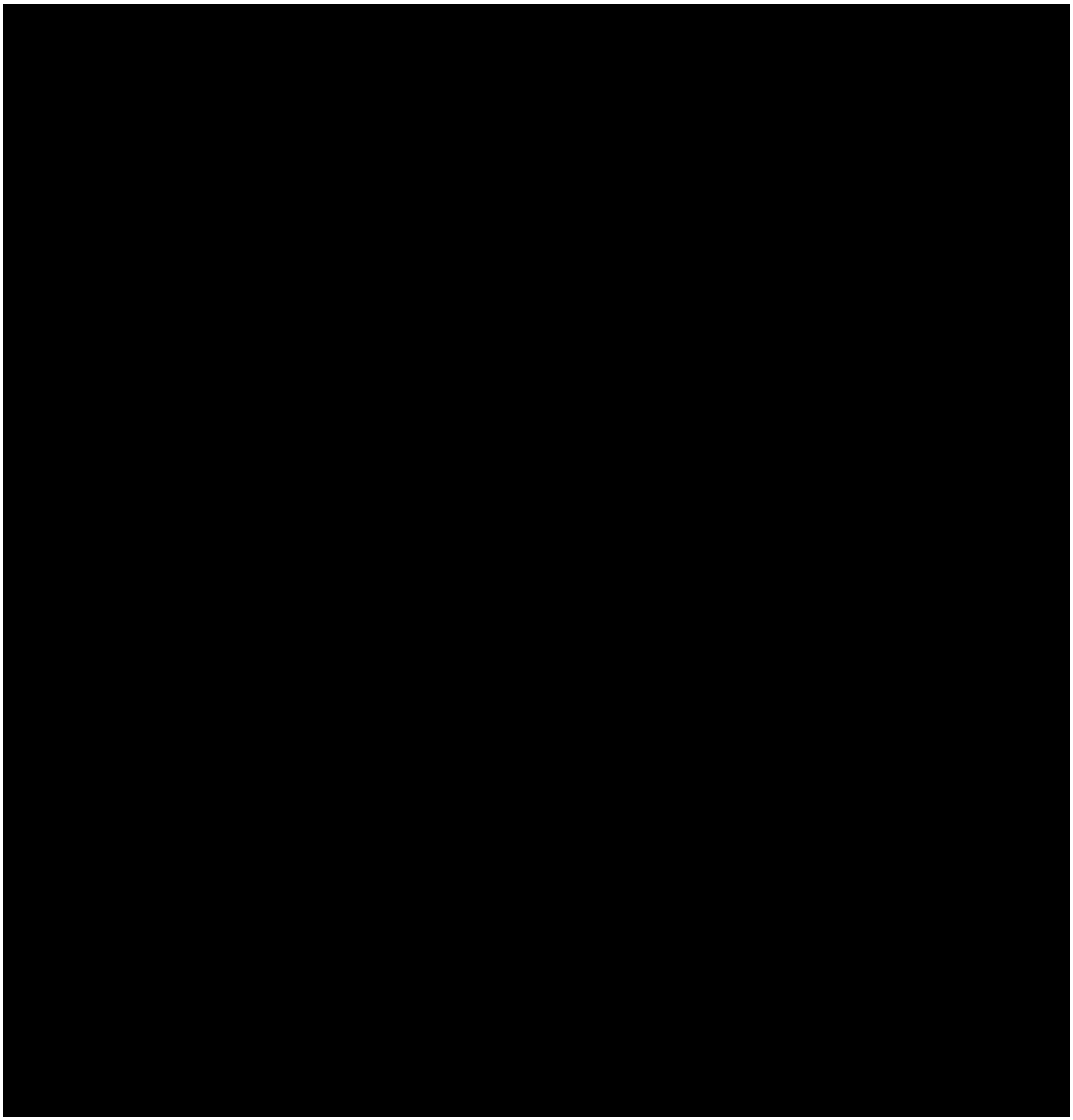
2. Enthesitis (yes, no)
3. ACR50 response (yes, no)
4. ACR70 response (yes, no)
5. Minimal Disease Activity (yes, no)
6. PASI75 response (yes, no)
7. PASI90 response (yes, no)
8. PASI100 response (yes, no)
9. Change from baseline in DAS28-CRP
10. Change from baseline in PASDAS
11. Change from baseline in SF12
12. Change from baseline in HAQ-DI

Two analyses of dactylitis and enthesitis (secondary efficacy variables 1 and 2) will be performed at each time point. For the first analysis, the data for the subgroup of patients who have dactylitis at baseline will be used (similarly for enthesitis) and the analysis of the binary response variable (yes, no) will be similar to the analysis of secondary efficacy variables 3-8 below. In the supporting analysis, the data for all patients will be used and an ordinal variable will be created based on presence (yes) or absence (no) of dactylitis at baseline and a post-baseline visit (similarly for enthesitis). The three categories for the ordinal variable will be no/no (category 1), no/yes and yes/no (category 2), and yes/yes (category 3). This ordinal response variable will be analyzed using a proportional odds regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight as explanatory variables (Stokes, Davis, and Koch, 2012). The odds ratios for each dose of secukinumab versus placebo, 95% confidence intervals for the odds ratios, and p-values based on the fitted model will be reported.

Secondary efficacy variables 3-8 will be analyzed at each time point using a logistic regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight as explanatory variables (Stokes, Davis, and Koch, 2012). The odds ratios for each dose of secukinumab versus placebo, 95% confidence intervals for the odds ratios, and p-values based on the fitted model will be reported.

Secondary efficacy variables 9-12 will be analyzed at each time point by an analysis of covariance (ANCOVA) model with treatment (3 treatment groups), baseline, methotrexate usage at baseline (yes, no), and body weight as explanatory variables. The least squares means of the three treatment groups, least squares mean differences between each dose of secukinumab and placebo, 95% confidence intervals for the difference between each dose of secukinumab and placebo, and p-values based on the fitted linear model will be reported. Missing data will be imputed using the last-observation-carried-forward (LOCF) method.

Analyses of the secondary efficacy variables will be based on the Full Analysis Set.



9.5.2 Safety variables

The assessment of safety will be based mainly on the frequency of adverse events and laboratory data. Other safety data (e.g., vital signs and special tests) will be considered, as appropriate.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (e.g., severity or relatedness to study medication) will be listed, as appropriate.

Adverse events and serious adverse events up to and including Week 16 visit will be included in the database for the analysis at the primary analysis time point (Week 16). All Adverse events and serious adverse events will be included in the final database analysis (Week 52).

Laboratory variables will be summarized.

Analysis of safety data will be based on the Safety Set.

9.6 Interim analyses

The database of this study will be locked twice, first after the end of Treatment Period 1 (Week 16) and again after the end of Treatment Period 2 (Week 52). Data analyses will follow each database lock. The main analysis (or test) for the primary objective will be done at Week 16. As Week 16 is the primary analysis time point, no adjustment to the significance level of 0.05 will be made.

9.7 Sample size calculation

The sample size was calculated based on the primary efficacy variable (i.e., ACR20 response) for the primary comparison (i.e., secukinumab 300 mg versus placebo). ACR20 response rates of 50% for secukinumab 300 mg and 20% for placebo (corresponding to an odds ratio of 4) at Week 16 were assumed, based on results from AIN457F2312 (FUTURE 2) study. Using a continuity-corrected chi-squared test, an allocation ratio of 2:1, a two-sided significance level of 0.05, and a power of 0.90, approximately 88 patients in secukinumab 300 mg group and 44 patients in placebo group will be needed (nQuery Advisor 7.0). Assuming a loss to follow-up rate of 10% and a 2:2:1 allocation ratio (secukinumab 300 mg: secukinumab 150 mg: placebo), the total number of randomized patients will be approximately 250 (100 on secukinumab 300 mg, 100 on secukinumab 150 mg, and 50 on placebo)

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

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

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

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

11 Protocol adherence

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

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis

[redacted]

and approved by the IRB/IEC and health authorities, where required, it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

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

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12.1 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests. Whether or not any action needs to be taken to address notable laboratory or vital signs values will be determined by the investigator/qualified site staff, taking into

[redacted]

account the overall status of the subject. No specific action is pre-defined within this study protocol.

Liver function and related variables

ALT (SGPT)	> 3 x Upper Limit of Normal (ULN)
AST (SGOT)	> 3 x ULN
Total bilirubin	> 1.5 x ULN
Alkaline phosphatase	> 2 x ULN

Renal function and electrolyte variables

Creatinine (serum)	> 1.5 x ULN

Hematology values

Hemoglobin	≥ 2.0 g/dL decrease from baseline
Platelet count	< Lower Limit of Normal (LLN)
White blood cell	< 0.8 x LLN
Neutrophils	< 0.9 x LLN
Eosinophils	> 1.1 x ULN
Lymphocytes	> 1.1 x ULN

12.2 Appendix 2: The classification criteria for psoriatic arthritis (CASPAR)

To meet the Classification of Psoriatic Arthritis (CASPAR) criteria for diagnosis of psoriatic arthritis according to (Taylor 2006), a subject 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 (**2 points**)
   - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.†
   - 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.
   - A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.
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**)

[redacted]

4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist (**1 point**)
5. Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot (**1 point**)

Total score: _____

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

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

12.4 Appendix 4: American College of Rheumatology (ACR) Measures and Criteria of Response

Number of tender joints:

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

The 78 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 2 first carpometacarpal, 10 metacarpophalangeal, 10 proximal interphalangeal, 8 distal interphalangeal joints of the hands, the 2 hip, 2 knee, 2 talo-tibial, 2 mid-tarsal, 10 metatarsophalangeal, 10 proximal interphalangeal, and 8 distal interphalangeal 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 PsA pain

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

Patient's global assessment of disease activity

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

Physician's global assessment of disease activity

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

Patient's assessment of physical function

Health Assessment Questionnaire – HAQ-DI©

ACR20/50/70*

A patient will be considered as improved according the ACR20 criteria* if she/he has at least 20 % improvement in the two following measures:

- Tender joint count,
- Swollen joint count.
- and at least 3 of the following 5 measures:
  a. Patient's assessment of pain,
  b. Patient's global assessment of disease activity,
  c. Physician's global assessment of disease activity,
  d. Health Assessment Questionnaire (HAQ©) score,
  e. C-reactive protein (CRP)/Erythrocyte Sedimentation Rate (ESR).

ACR50 = 50 % improvement in at least 3 of the 5 measures and 50 % improvement in the swollen and tender joint count.

ACR70 = 70 % improvement in at least 3 of the 5 measures and 70 % improvement in the swollen and tender joint count.

Reference: (Felson 1995)

12.5 Appendix 5: Disease Activity Score (DAS)

The Disease Activity Score (DAS) is a combined index to measure the disease activity in patients with RA. It has been extensively validated for its use in clinical trials in combination with the EULAR response criteria.

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Evaluation of response to a treatment can be made much easier and more objective using the DAS. Just assess the number of swollen and tender joints and measure the ESR. The DAS will provide you with a number between 0 and 10, indicating how active the disease is at this moment. Recently the DAS-CRP has been developed. The C-reactive protein (CRP) may be used as an alternative to ESR in the calculation of the DAS or the DAS28.

Using the DAS, several thresholds have been developed for high disease activity, low disease activity or remission. Also response criteria have been developed based on the DAS, so when the DAS of a patient is measured at two time-points (e.g. before the start of a treatment and after 3 months), the patients clinical response can be assessed.

The DAS in the clinical trials

Comparing the DAS28 from one patient on two different time-points, it is possible to define improvement or response. The EULAR response criteria are defined as follows:

Present DAS28	DAS28 improvement		
	>1.2	0.6 - 1.2	<0.6
<3.2	good response	moderate response	no response
3.2 - 5.1	moderate response	moderate response	no response
>5.1	moderate response	no response	no response

Both the thresholds for high and low disease activity and remission and the abovementioned improvement criteria should give you a feel how to interpret your DAS28 scores.

In order to calculate the DAS28, information about the following disease variables is needed:

- The number of swollen joints and tender joints should be assessed using 28-joint count (tender28 and swollen28).
- The erythrocyte sedimentation rate (ESR) should be measured in mm/hour.
- The patient's general health (GH) or global disease activity measured on a Visual Analogue Scale (VAS) of 100 mm (both are useable for this purpose) must be obtained.

Using this data, the DAS28 can be calculated using the following formula:

DAS28 = 0.56 * sqrt(tender28) + 0.28 * sqrt(swollen28) + 0.70 * ln(ESR) + 0.014 * GH

The DAS28 provides you with a number on a scale from 0 to 10 indicating the current activity of the rheumatoid arthritis of your patient. A DAS28 above 5.1 means high disease activity whereas a DAS28 below 3.2 indicates low disease activity. Remission is achieved by a DAS28 lower than 2.6 (comparable to the PsA remission criteria).

Disease Activity Scores using C-reactive protein

C-reactive protein (CRP) may be used as an alternative to ESR in the calculation of the DAS or DAS28, using the formulas below. CRP is a more direct measure of inflammation than ESR, and it is more sensitive to short-term changes (Kushner 1991). CRP production is

[redacted]

associated with radiological progression in RA (Van Leeuwen 1993), and is considered at least as valid as ESR to measure RA disease activity (Mallya 1982, Wolfe 1997). Another advantage of determination of CRP is that waiting time for the laboratory result is shorter and that in case of multicenter studies a central laboratory can be used.

The following formulas to calculate the DAS28 using CRP (mg/L) give good estimations of the original DAS28 values on a group level. **DAS28-4(crp) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP+1) + 0.014*GH + 0.96**

TJC28: 28 Tender joint count; SJC28: 28 Swollen joint count; CRP: C-reactive protein; GH: General Health on a 100mm. Visual Analogue Scale.

It is strongly advised to adhere either to ESR or to CRP determinations.

[redacted]

12.6 Appendix 6: The Psoriasis Area and Severity Index (PASI)

PASI Scoring Worksheet

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

a. Divide body into four areas: head, arms, trunk to groin, and legs to top of buttocks.
b. Generate an average score for the erythema, thickness, and scale for each of the 4 areas (0=clear, 1-4=increasing severity).
c. Sum scores of erythema, thickness, and scale for each area.
d. Generate a percentage for skin covered with psoriasis for each area and convert that to a 0-6 scale. ‡
e. Multiply score of item c above times item d above for each area and multiply that by 0.1, 0.2, 0.3 and 0.4 for head, arms, trunk, and legs, respectively.
f. Add these scores to get the PASI score.

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

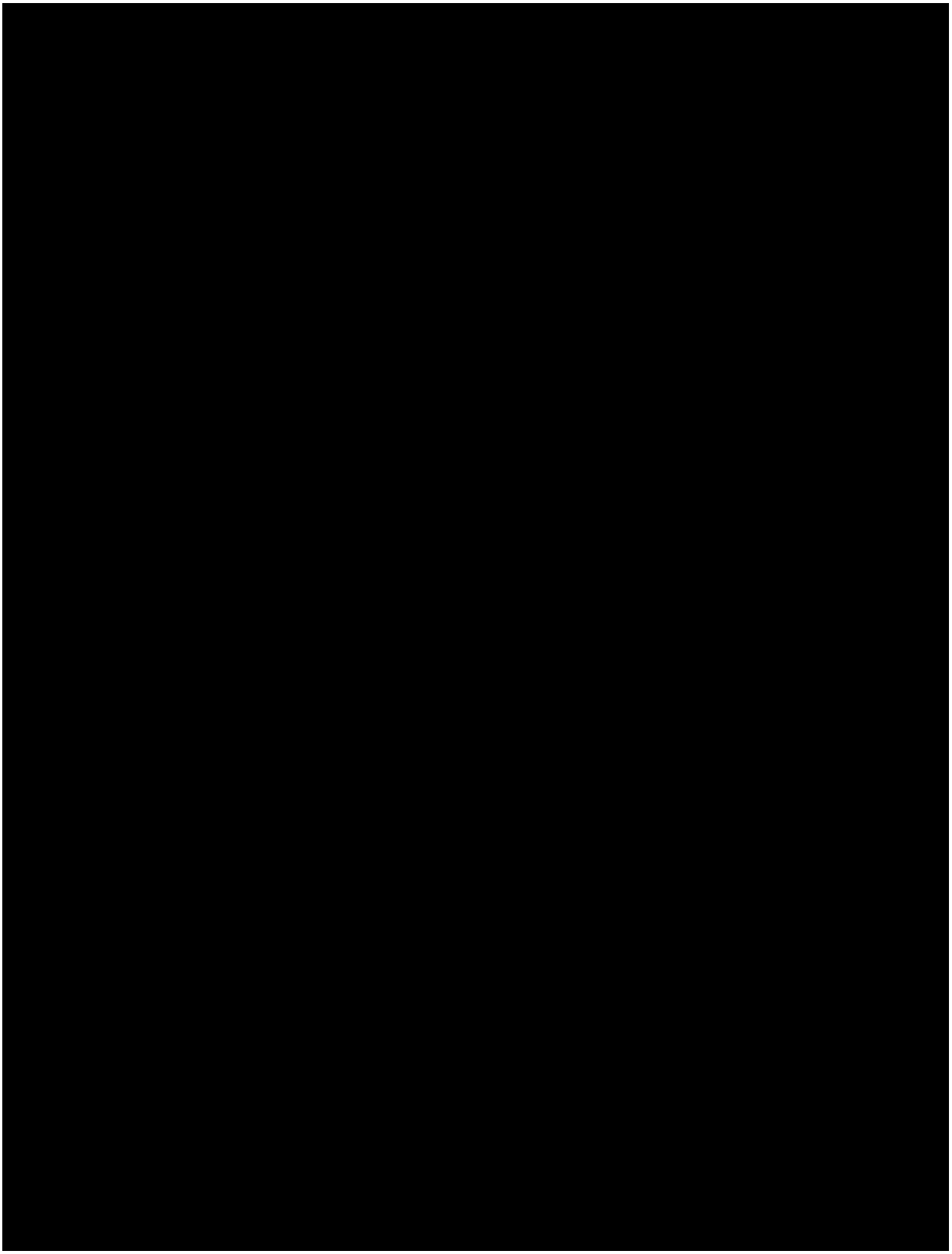
‡Area scoring criteria (score: % involvement)

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

Derived from Feldman SR and Krueger GG (2005). Psoriasis assessment tools in clinical trials. Ann Rheum Dis; 64: ii65-ii68.

[redacted]

[redacted]



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12.8 Appendix 8: Health Assessment Questionnaire (HAQ)

The HAQ© (Fries JF et al. 1980) is a validated measure of physical disability and functional status. It has four dimensions: disability, pain, drug side effects and dollar costs, although, the latter three 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 four response categories, ranging from 'without any difficulty' to 'unable to do'. The ACR Rheumatology Committee on Outcome Measures in RA recommends the use of this questionnaire in clinical trials.

Scoring of the HAQ©

The HAQ© will be scored in accordance with the recommendation from the developers outlined in the "HAQ PACK" from Stanford University, California.

The following coding is to be used for the 8 categories of the disability outcome dimension:

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

Within each of the 8 categories only the item indicating the most severe impairment contributes to the category score. If the patient requires the use of aids, devices, or help from another to accomplish any of the activities in an associated category, then the score for that category will be assigned the value 2, unless the score is already 3 (i.e. scores of 0 or 1 are increased to 2). Associated categories are defined in the "HAQ PACK". From the scores for each category a Standard Disability Index (SDI) is computed by summing the computed scores for each category and dividing by the number of categories answered. The SDI is not

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computed if the patient does not have scores for at least 6 categories. This SDI is the HAQ© score, which will be used in the statistical analyses of this instrument. The range for this score is (0, 3).

HAQ© Data Collection

The HAQ© is to be completed by the patients in their local languages, using an electronic device. The questionnaires should be completed by the patients in a quiet area free from disturbance, and before any visit assessments. Patients should receive no help from family members; if questions cannot be answered alone (due to problems with reading or understanding), then the doctor or nurse should read the questions and record the patient's responses without influencing their answers. The information provided is strictly confidential and will be treated as such. If a patient has missed a question or given more than one response per question, then this should be brought to patient. Incomplete questions should not be accepted without first encouraging the patient to complete unanswered questions.

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

[redacted]

12.10 Appendix 10: Guidelines for administering the PRO questionnaires

Before trial start

PROs will be administered to patients using an electronic tablet called a SitePad

Study coordinators should familiarize themselves with the PRO questionnaire(s) in the trial and identify any items where a patient's response might highlight issues of potential concern. *For example, one question in the SF-12 'How much of the time in the past 4 weeks- have you felt downhearted and blue?' If a patient responds 'most or all of the time', then the study coordinator should inform the study investigator.*

Before completion

1. The SitePad will have the correct Questionnaires for the patients, at the appropriate visits, and in the appropriate language.
   -
2. Patients should have adequate space and time to complete their questionnaires on the SitePad
3. Questionnaires should be administered and completed before the clinical examination

During completion

1. Administrator may clarify the questions but should not influence the response
2. The SitePad will only allow one response for each question
3. Also see 'Addressing Problems and Concerns'

After completion

1. The Patient's data/reports **MUST** be transmitted so it can be reviewed in StudyWorks.

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

Addressing Problems and Concerns

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

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

Tell the patient that completion of the questionnaire(s) is voluntary but is an important part of their participation in the study. The goal of these questionnaires is to better understand the physical, mental, and social health problems of patients. Emphasize that this information is as important as any of the other medical information, and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the respondent has filled in the past. If the patient still declines, please ask them to complete the end of visit

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questionnaire which confirms they have declined to complete the questionnaires. Thank the patient. **The patient is too ill or weak to complete the questionnaire(s)**

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

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

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

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

If non-completion is a result of the patient having trouble understanding particular items, ask the patient to explain the difficulty. Re-read the question for them *verbatim*, but do not rephrase the question. If the respondent is still unable to complete the questionnaire, that questionnaire will be forfeited since partial response will not be saved. Thank the patient.

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

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

The patient asks the meaning of a question/item

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

General Information about all questionnaire(s):

All questionnaires are to be completed by the patients on the SitePad. The questionnaires should be completed by the patients in a quiet area free from disturbance, and before any visit assessments. Patients should receive no help from family members; if questions cannot be answered alone (due to problems with reading or understanding), then the doctor or nurse should read the questions verbatim without influencing their answers. The information provided is strictly confidential and will be treated as such.

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The investigator must complete the patient/visit information on the SitePad and ensure that the center number, patient's number and initials are identical to the electronic Case Record Form. As there are no source data for the questionnaires, the data queries will be restricted to patient/visit information

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