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Secukinumab (AIN457)

Clinical Trial Protocol CAIN457P12302 / NCT04209205

A randomized, double-blind, placebo-controlled, parallel group, phase III multicenter study of intravenous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in subjects with active Psoriatic Arthritis

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List of abbreviations

ACR	American College of Radiology
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
b.i.d.	twice a day
[redacted]	[redacted]
BDR	Bioanalytical Data Report
BMI	Body Mass Index
BSA	Body surface area
BSL	Baseline
CFR	Code of Federal Regulation
C_{max}	Maximum concentration
$C_{max,ss}$	Maximum concentration steady-state
C_{min}	Minimum concentration
$C_{min,ss}$	Minimum concentration steady-state
CMO&PS	Chief Medical Office and Patient Safety
COAs	Clinical Outcome Assessments
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical study report
CTC	Common Toxicity Criteria
DMARD	Disease Modifying Anti-rheumatic Drug
DSUR	Development Safety Update Report
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EMA/EMEA	European Medical Agency
ESR	Erythrocyte sedimentation rate
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GWA	genome-wide association
HAQ-DI	Health Assessment Questionnaire – Disability Index
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein

HIV	human immunodeficiency virus
hsCRP	high sensitivity C-Reactive Protein
i.v.	intravenous
IB	investigator brochure
IBD	inflammatory bowel disease
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVR	Interactive Voice Response
LDI	Leeds Dactylitis Index
LDL	Low-density lipoprotein
LEI	Leeds Enthesitis Index
LFT	Liver function test
LLN	Lower limit of normal
LLQ	Lower limit of quantification
MCR	Major Clinical Response
MCS	Mental Component Summary
MDA	minimal disease activity
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMP	Matrix Metalloproteinase
MMRM	Mixed effect Repeated Measures model
mNAPSI	Modified Nail Psoriasis Severity Index
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NSAID	Non-Steroidal Anti-Inflammatory Drug
o.d.	once a day
p.o.	oral
PA	posteroanterior
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
[redacted]	[redacted]
[redacted]	[redacted]
PPD	Purified Protein Derivative
PRO	Patient Reported Outcome
PsA	Psoriatic arthritis
QMS	Quality Management System
RBC	red blood cell(s)

RF	Rheumatoid factor
s.c.	subcutaneous
SAE	serious adverse event
SCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SJC	Swollen Joint Count
SNP	single nucleotide polymorphism
[redacted]	[redacted]
SST	Serum separator tube
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TFQ	Trial feedback Questionnaire
TJC	Tender Joint Count
TNF/TNFα	Tumor Necrosis Factor
TNF-IR	TNFα Inhibitor Incomplete Responder
ULN	upper limit of normal
UV	ultraviolet
VAS	Visual Analog Scale
WBC	white blood cell(s)
WHO	World Health Organization
[redacted]	[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
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 other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.

Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CAIN457P12302
Full Title	A randomized, double-blind, placebo-controlled, parallel group, phase III multicenter study of intravenous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in subjects with active Psoriatic Arthritis
Brief title	Study to demonstrate the efficacy, safety and tolerability of intravenous secukinumab up to 52 weeks in subjects with active Psoriatic Arthritis
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this global study is to provide up to 52 weeks of efficacy, safety and tolerability data to support registration of intravenous (i.v.) secukinumab (Initial dose of 6 mg/kg at Baseline (BSL) followed thereafter with 3 mg/kg administered every four weeks) in patients with active psoriatic arthritis (PsA) despite current or previous NSAID, DMARD and/or anti-TNF therapy. Efficacy and safety data from this clinical study will be used to support the registration of i.v. secukinumab in the US and other countries for treatment of patients with active psoriatic arthritis.

Primary Objective(s)	To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo in subjects with active psoriatic arthritis (PsA) based on the proportion of patients achieving an American College of Rheumatology 50 (ACR50) response.
Secondary Objectives	The efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects achieving an ACR20 response. The efficacy of i.v secukinumab at Week 16 is superior to placebo based on the proportion of patients achieving Minimal Disease Activity MDA 5/7. The efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects achieving a PASI90 response in the subgroup of subjects who have ≥3% skin involvement with psoriasis. The improvement (change) from baseline on i.v. secukinumab is superior to placebo for the PASDAS at Week 16. The improvement (change) from baseline on i.v. secukinumab is superior to placebo for the HAQ-DI at Week 16. The improvement (change) from baseline on i.v. secukinumab is superior to placebo for the SF36-PCS at Week 16. The improvement (change) from baseline on i.v. secukinumab is superior to placebo for the FACIT-fatigue at Week 16. The improvement (change) from baseline on i.v. secukinumab is superior to placebo for the mNAPSI at Week 16 for the subgroup of patients with nail involvement.

	The efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects with resolution of dactylitis by the Leeds Dactylytis Index in the subset of subjects who have dactylitis at baseline. The efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects with resolution of enthesitis by the Leeds Enthesitis Index in the subset of subjects who have enthesitis at baseline. The overall safety and tolerability of i.v. secukinumab compared to placebo as assessed by vital signs, clinical laboratory values, and adverse events monitoring.
Study design	This multicenter study uses a randomized, double-blind, placebo-controlled, parallel-group design. A screening (SCR) period running up to 10 weeks before randomization will be used to assess subject eligibility followed by a treatment period of 52 weeks. At baseline, approximately 380 patients with active psoriatic arthritis will be randomized to one of the two treatment groups in a 1:1 randomzation: Group 1: Approximately 190 patients with active psoriatic arthritis; These patients will receive secukinumab 6 mg/kg i.v. at BSL, followed by the administration of secukinumab 3 mg/kg i.v. every four weeks starting at Week 4. Group 2: Approximately 190 patients with active psoratic arthritis; These patients will receive i.v. placebo at BSL and at Weeks 4, 8, and 12, followed by the administration of secukinumab 3 mg/kg i.v. every four weeks starting at Week 16. Study will consist of 4 periods: a screening period (up to 10 weeks), treatment period 1 (total duration of 16 weeks) and treatment period 2 (total duration of 36 weeks) followed by a safety follow up period of 8 weeks after the end of treatment visit (i.e., Week 52). Primary endpoint analysis will be performed with Week 16 data (last patient completing Treatment period 1 (Week 16). Long-term efficacy and safety assessments will be performed up to Week 52.
Population	The study population will consist of male or female subjects at least 18 years of age, fulfilling the Classification criteria for Psoriatic Arthritis (CASPAR), and PsA for at least 6 months and have active PsA disease defined as ≥3 swollen and ≥3 tender joints. Subjects must report active disease despite current or previous NSAIDs, DMARDs and / or TNF inhibitor therapy or intolerance to these therapies. Concomitant therapy with MTX (≤25 mg/week) will be acceptable, if dose has been stable for at least four weeks prior to the randomization visit and should remain on a stable dose up to Week 16. Randomization will be stratified by previous TNFα inhibitor-use (TNFα inhibitor-naïve vs. TNFα inhibitor-inadequate responder).
Key Inclusion criteria	Subjects eligible for inclusion in this study have to fulfill all of the following criteria: Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have at BSL ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit counts as one joint each). Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies negative at screening.

	Subjects with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs. Subjects 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. Subjects taking corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 16. Subjects taking MTX (≤ 25 mg/week) are allowed to continue their medication if the dose and route of administration is stable for at least 4 weeks before randomization and should remain on a stable dose up to Week 16.
Key Exclusion criteria	Patients fulfilling any of the following criteria are not eligible for inclusion in this study: 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 Subjects taking high potency opioid analgesics (e.g. methadone, hydromorphone, morphine) Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor Ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, UV therapy) at randomization. The following wash-out periods need to be observed: 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 Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization. Subjects who have previously been treated with more than 3 different TNF inhibitors (investigational or approved). Subjects who have ever received biologic immunomodulating agents, investigational or approved except for those targeting TNFα. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
Study treatment	At baseline, eligible subjects will be randomized to one of the following two treatment arms in a 1:1 ratio Group 1: secukinumab i.v. (6 mg/kg) at BSL, followed by secukinumab 3 mg/kg i.v. every four weeks starting at Week 4 through Week 48 (exposure through week 52). Group 2: placebo i.v. at BSL, Week 4, 8 and 12 followed by secukinumab 3 mg/kg i.v. every four weeks starting at Week 16 through Week 48 (exposure through week 52).

Efficacy assessments	Key assessments for ACR response (Primary Objective) Swollen Joint Count (SJC)/Tender Joint Count (TJC) Patient's global assessment of disease activity (VAS) Physician's global assessment of disease activity (VAS) Patient's assessment of PsA pain intensity (VAS) Health Assessment Questionnaire – Disability Index (HAQ-DI©) high sensitivity C-Reactive Protein (hsCRP) and/ or Erythrocyte Sedimentation Rate (ESR) Key assessments for Secondary Objectives: Minimal disease activity Psoriasis Area and Severity Index (PASI) Psoriatic Arthritis Disease Activity Score (PASDAS) Health Assessment Questionnaire – Disability Index (HAQ- DI) Short Form Health Survey (SF-36) Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Modified Nail Psoriasis Severity Index (mNAPSI) Leeds Dactylitis Index (LDI) Leeds Enthesitis Index (LEI)
Key safety assessments	Following are the key safety assessments: Evaluation of AE's/ SAE's Physical examination and Vital signs QuantiFERON TB-Gold test or PPD skin test Electrocardiogram Local tolerability (Injection site reactions) Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis and cardiovascular panel) [redacted]
Other assessments	Quality of Life questionnaires/ Patient reported outcomes (PROs) [redacted]
Data analysis	The primary endpoint in the study is the proportion of subjects who achieve an ACR50 response at Week 16. The statistical hypothesis for ACR50 being tested is that there is no difference in the proportion of subjects fulfilling the ACR50 criteria at Week 16 in the i.v. regimen vs. placebo. Let P_j denote the proportion of ACR50 responders at Week 16 for treatment regimens $j, j = 0, 1$ where --0 corresponds to placebo, --1 corresponds to i.v. regimen In statistical terms, $H_1: P_1 = P_0$, $H_{A1}: P_1 \neq P_0$, for the i.v. secukinumab regimen, i.e. H_1: i.v. regimen is not different to placebo for signs and symptoms (ACR50 response) at Week 16

	The primary endpoint of ACR50 at Week 16 in the FAS will be evaluated using a logistic regression with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate. Marginal response proportion will be computed for comparisons of i.v. regimen vs. placebo utilizing the logistic regression model fitted. Safety analyses will include summaries of AEs, laboratory measurements, and vital signs.
Key words	Active Psoriatic Arthritis, Intravenous secukinumab

1 Introduction

1.1 Background

Psoriatic arthritis (PsA) is a chronic immune-mediated disease encompassing a spectrum of overlapping clinical entities (Moll and Wright 1973). About 10 - 40% of patients with psoriasis suffer from PsA. Efforts were aimed at defining more stringent classification criteria for standardized recruitment into clinical trials (McGonagle and Tan 2007). PsA is associated with significant morbidity and disability, and thus constitutes a major socioeconomic burden. It is not only more common but also more severe than previously thought (Gladman 1990). The majority of patients will have psoriasis prior to the occurrence of the associated arthritis and are typically under treatment for their skin disease. For musculoskeletal disease manifestations, initially NSAIDs are used to alleviate symptoms. Typically disease modifying anti-rheumatic drugs (DMARDs) are used for PsA, including methotrexate (MTX), sulfasalazine, cyclosporine, and leflunomide; however, these are often inadequate because they only partially control established disease (Mease 2008).

Psoriatic arthritis (PsA) referred to as spondyloarthritides (SpA). The scientific community is split over the question whether to view these conditions together or consider them as separate entities (Nash et al 2005). For example, inflammatory back pain associated with psoriasis fit two classifications (1) Ankylosing spondylitis with psoriasis or (2) psoriatic spondylitis (Gladman 2007). However, while 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 (SNP) scan study, where IL-23R variants that were previously linked to Crohn`s disease and psoriasis (diseases that may both co-exist with spondylarthritides) conferred risk to developing ankylosing spondylitis (Barrett et al 2008). Together, a common pathway including the IL-23/IL-17 axis have been shown to play a role in seronegative SpAs including psoriatic arthritis.

Several lines of evidence support the notion of prominent T cell involvement in the pathogenesis of PsA. Memory CD4+ and CD8+ cells are present in skin lesions as well as the inflamed synovium that express activation markers and have characteristics of oligoclonal expansion (Curran et al 2004, Tassiulas et al 1999). Clinical trials demonstrated efficacy of T cell targeted therapy in PsA (cyclosporine A, CTLA4 Ig, alefacept). TNF-blocking therapy was successfully introduced to the treatment of patients with PsA (Mease et al 2000). Despite these efforts, an unmet clinical need exists for patients with PsA for better disease control and long-term prevention of structural damage beyond mere abrogation of inflammatory processes. Thus, current treatment options for patients with intolerance or an inadequate response to anti--TNF-α agents are limited.

IL-17 antagonism represents a therapeutic approach aimed at interference with the chronic inflammatory process by selectively targeting the predominant proinflammatory cytokine of the helper Th17 cell subset. Additional effects of anti-IL17 on bone homoeostasis via RANKL (Receptor activator of nuclear factor kappa-B ligand) 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 prevent structural damage 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 which is thought to be an important mediator of autoimmunity. Neutralization of IL-17A has strong pre-clinical and clinical target validation, and documentation of efficacy in a proof of concept study (CAIN457A2101) and pivotal registration studies in PsA (CAIN457F2306 and CAIN457F2312). Registration studies conducted in patients with PsA suggest that a clinically meaningful response for signs and symptoms is induced as early as 2 weeks after start of secukinumab treatment, with further improvement up to Week 6 and maintenance of response up to Week 16.

In several large placebo-controlled Phase 3 studies (CAIN457F2306, CAIN457F2306E1, CAIN457F2312, CAIN457F2318, CAIN457F2336 and CAIN457F2342), secukinumab consistently demonstrated both statistically significant and clinically meaningful differences in ACR20 response compared to placebo in adult patients with active PsA. The majority of patients treated with the recommended 150 mg and 300 mg regimens achieved an ACR20 response in joint-related signs and symptoms, achieved benefit in skin endpoints (as shown by PASI 75, PASI 90 response rates and IGA mod 2011 0 or 1 response), improvement in physical function, improvement in quality of life and inhibition of structural progression. Statistical significance of secukinumab vs placebo at Week 16/24 for the primary endpoint and most secondary endpoints was achieved in all five PsA phase 3 trials.

In Studies CAIN457F2312, CAIN457F2318, CAIN457F2336 and CAIN457F2342 dose escalation from 150 mg to 300 mg had pronounced efficacy improvements in patients with low response levels at the time of dose escalation. These improvements were sustained across many endpoints assessing both skin and arthritic components of PsA (e.g., ACR, PASI, DAS28-CRP, SF36). Therefore, treatment with secukinumab may also reduce loss of cartilage and erosion of bone in PsA and may result in improvement of symptoms and functional joint manifestations in afflicted patients.

As of 25 June 2019, over 27,000 subjects have been enrolled in studies with secukinumab with over 22,000 having received active drug at doses ranging from single and/or multiple doses of 0.1 mg/kg to 30 mg/kg intravenous and 25 mg to 300 mg subcutaneous. Overall, healthy subjects and patients have received secukinumab across various indications (RA, AS, PsA, multiple sclerosis, uveitis, Crohn's disease, dry eye, and polymyalgia rheumatica) at doses ranging from single and multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25 mg to 300 mg s.c. Full safety results from all completed studies show comparable numbers of adverse events in subjects treated with secukinumab compared to placebo without indication of any specific organ toxicity.

A more detailed review of the pre-clinical and clinical information on secukinumab is available in the Investigators Brochure.

Previous registration and other Phase 3 studies have used mainly subcutaneous administration preceded by Intravenous (i.v.) or Subcutaneous (s.c.) loading while this study is posited to now explore the efficacy and safety with i.v. administration of secukinumab.

1.2 Purpose

The purpose of this global study is to provide up to 52 weeks of efficacy, safety and tolerability data to support the registration of intravenous (i.v.) secukinumab (initial dose of 6 mg/kg at baseline (BSL) followed thereafter with 3 mg/kg administered every four weeks) in patients with active psoriatic arthritis (PsA) despite current or previous NSAID, DMARD and/or anti-TNF therapy.

Efficacy and safety data from this clinical study will be used to support the registration of i.v. secukinumab in the US and other countries for treatment of patients with active psoriatic arthritis.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo in subjects with active psoriatic arthritis (PsA) based on the proportion of patients achieving an American College of Rheumatology 50 (ACR50) response.	• A subject is defined as an ACR50 responder if, and only if, the following three conditions hold: 1. they have a ≥ 50% improvement in the number of tender joints (based on 78 joints) 2. they have a ≥ 50% improvement in the number of swollen joints (based on 76 joints) 3. they have a ≥ 50% 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 – Disability Index (HAQ-DI©) score • Acute phase reactant (hsCRP or ESR)

Objective(s)	Endpoint(s)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• The efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects achieving an ACR20 response.	• ACR20 = 20% improvement in at least 3 of the 5 measures and 20% improvement in the swollen and tender joint count.
• The efficacy of i.v secukinumab at Week 16 is superior to placebo based on the proportion of patients achieving Minimal Disease Activity MDA 5/7.	• Proportion of patients achieving MDA 5/7 defined as having met ≥5 of the following criteria: ≤1 tender joint, ≤1 swollen joint, PASI ≤1 or body surface area ≤3%, patient assessment of pain (VAS) ≤15, patient global assessment of disease (VAS) ≤20, HAQ-DI ≤0.5, tender entheseal points ≤1).
• The efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects achieving a PASI90 response in the subgroup of subjects who have ≥3% skin involvement with psoriasis.	• The proportion of patients achieving a 90% reduction of the PASI score in patients with ≥ 3% body surface area (BSA) psoriasis at baseline.
• The improvement (change) from baseline on i.v. secukinumab is superior to placebo for the PASDAS at Week 16.	• Change in PASDAS score relative to baseline.
• The improvement (change) from baseline on i.v. secukinumab is superior to placebo for the HAQ-DI at Week 16.	• Assess the functional ability of subjects with PsA using the Health Assessment Questionnaire – Disability Index (HAQ- DI) relative to baseline.
• The improvement (change) from baseline on i.v. secukinumab is superior to placebo for the SF36-PCS at Week 16.	• Absolute and percent change from baseline in SF-36 Physical Component Score.
• The improvement (change) from baseline on i.v. secukinumab is superior to placebo for the FACIT-fatigue at Week 16.	• Absolute and percent change from baseline in FACIT-Fatigue scores.
• The improvement (change) from baseline on i.v. secukinumab is superior to placebo for the mNAPSI at Week 16 for the subgroup of patients with nail involvement.	• Change from baseline in mNAPSI score in patients with nail involvement.
• The efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects with resolution of dactylitis by the Leeds Dactylytis Index in the subset of subjects who have dactylitis at baseline.	• Proportion of patients with complete resolution of dactylitis as determined by the Leeds Dactylitis Index (LDI) in patients with dactylitis at baseline.
• The efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects with resolution of enthesitis by the Leeds Enthesitis Index in the subset of subjects who have enthesitis at baseline.	• Proportion of patients with complete resolution of enthesitis as determined by the Leeds Enthesitis Index (LEI) in patients with enthesitis at baseline.

Objective(s)	Endpoint(s)
• The overall safety and tolerability of i.v. secukinumab compared to placebo as assessed by vital signs, clinical laboratory values, and adverse events monitoring.	• Assessment of Physical exams, ECGs, vital signs, laboratory assessments.

[redacted]

[redacted]

3 Study design

This multicenter study uses a randomized, double-blind, placebo-controlled, parallel-group design to study the efficacy, safety and tolerability of treatment with intravenous secukinumab in patients with active PsA.

The study population comprises approximately 380 patients with active PsA, despite current or previous NSAID, DMARD and / or TNF inhibitor therapy or intolerance to these therapies.

At baseline, patients will be randomized to one of the two treatment groups in a 1:1 randomization:

- **Group 1:** approximately 190 patients; These patients will receive secukinumab 6 mg/kg i.v. at Baseline (BSL), followed by the administration of secukinumab 3 mg/kg i.v. every four weeks starting at Week 4.
- **Group 2:** approximately 190 patients; These patients will receive i.v. placebo at BSL, Weeks 4, 8, and 12, followed by the administration of secukinumab 3 mg/kg i.v. every four weeks starting at Week 16.

This study will consist of 4 periods: a screening period (up to 10 weeks), treatment period 1 (total duration of 16 weeks) and treatment period 2 (total duration of 36 weeks) followed by a safety follow up period of 8 weeks after the end of treatment visit (i.e., Week 52).

To ensure a balance across both arms, patients previously treated with TNF-inhibitors will be stratified at randomization. No more than 25% of previously treated TNF-inhibitor patients will be enrolled in the study, with this cutoff applied to each group at randomization (no more than 48 patients per group).

Because PsA is considered a chronic disease with no ‘true’ and lasting placebo response, all patients, including those on placebo, will switch to open-label i.v. secukinumab at Week 16. However, all patients and investigators/ site staff will remain blinded to the original randomized treatment group assignment (i.v. secukinumab treatment or placebo).

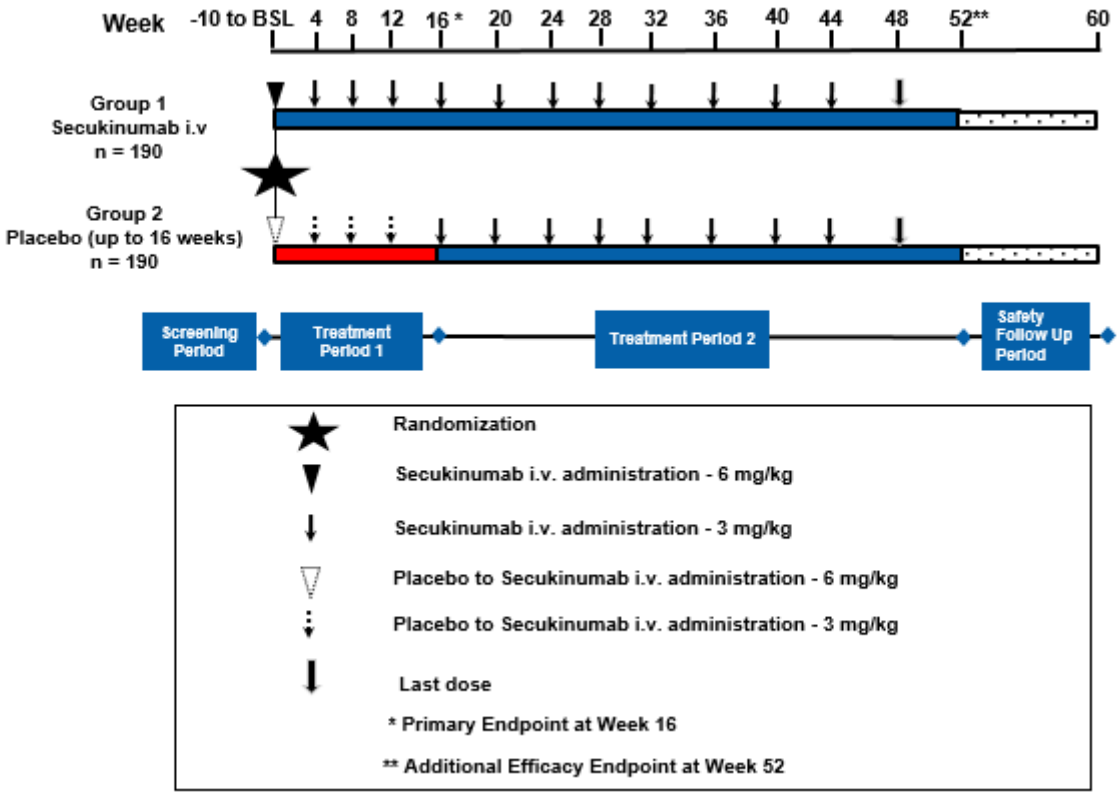
An end of treatment visit (Week 52) will be done 4 weeks after last study treatment administration, and a post treatment follow-up visit (Week 60) is to be done 8 weeks after end of the treatment visit for all subjects (regardless of whether they complete the entire study as planned or discontinue prematurely).

All intravenous infusions will be performed at the study site and site personnel will administer the infusions to subjects.

Rescue medication is not allowed until Week 16. However, subjects who are deemed by the investigator not to be benefiting from the study treatment based on safety and efficacy assessments or for any reason of their own accord will be free to discontinue participation in the study at any time.

The study will have a primary endpoint at Week 16. A Primary endpoint analysis will be performed with Week 16 data (last patient completing Treatment Period 1). Long-term efficacy and safety assessments will be performed up to Week 52.

Figure 3-1 Study Design



4 Rationale

4.1 Rationale for study design

4.1.1 Rationale for choice of background therapy

Traditional clinical management of PsA by pharmacotherapy involves the hierarchial use of NSAID's, DMARD's and TNF-inhibitor or anti-IL-17A inhibitor biologic therapies.

This study plans to enroll PsA patients with active disease, despite current or previous NSAIDs, DMARDs and/or TNF inhibitor therapy or intolerance to these therapies. A background of NSAID therapy and/or 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 randomization visit. Inclusion of patients with active PsA who have previously been treated with TNF inhibitors (up to 25% in each group) make the background patient population more representative of the real world clinical scenario.

4.2 Rationale for dose/regimen and duration of treatment

Phase 3 studies in subjects with active PsA (CAIN457F2312, CAIN457F2318 and CAIN457F2342) demonstrated the superior efficacy of secukinumab 150 mg s.c. and 300 mg s.c. regimens over placebo. Secukinumab 150 mg s.c. and 300 mg s.c. regimens had a rapid onset of response and similar magnitude of efficacy across several endpoints.

While secukinumab 150 mg s.c. and 300 mg s.c. regimens are both more efficacious than placebo regardless of TNF-naive or TNF-IR status, the 300 mg s.c. regimen provided the greatest efficacy across multiple PsA domains including ACR20, ACR50, [redacted]HAQ-DI, [redacted] PASI90, SF-36 PCS, in the resolution of dactylitis and enthesitis as well as in the inhibition of structural progression.

In a pooled analysis of 2049 patients with PsA in the phase III program, evidence of higher efficacy was shown in the overall population and several subsets of PsA patients including, but not limited to, TNF-IR patients and patients who do not use concomitant MTX, favoring secukinumab 300 mg s.c. over 150 mg s.c. at Week 16 for several endpoints. This trend was maintained up to Week 52.

Furthermore, secukinumab 300 mg s.c. was more efficacious than 150 mg s.c. in achieving clinically meaningful improvements in skin disease, particularly with respect to clear/almost clear skin (PASI90, [redacted]) in subjects with moderate to severe psoriasis (defined as ≥ 10% BSA).

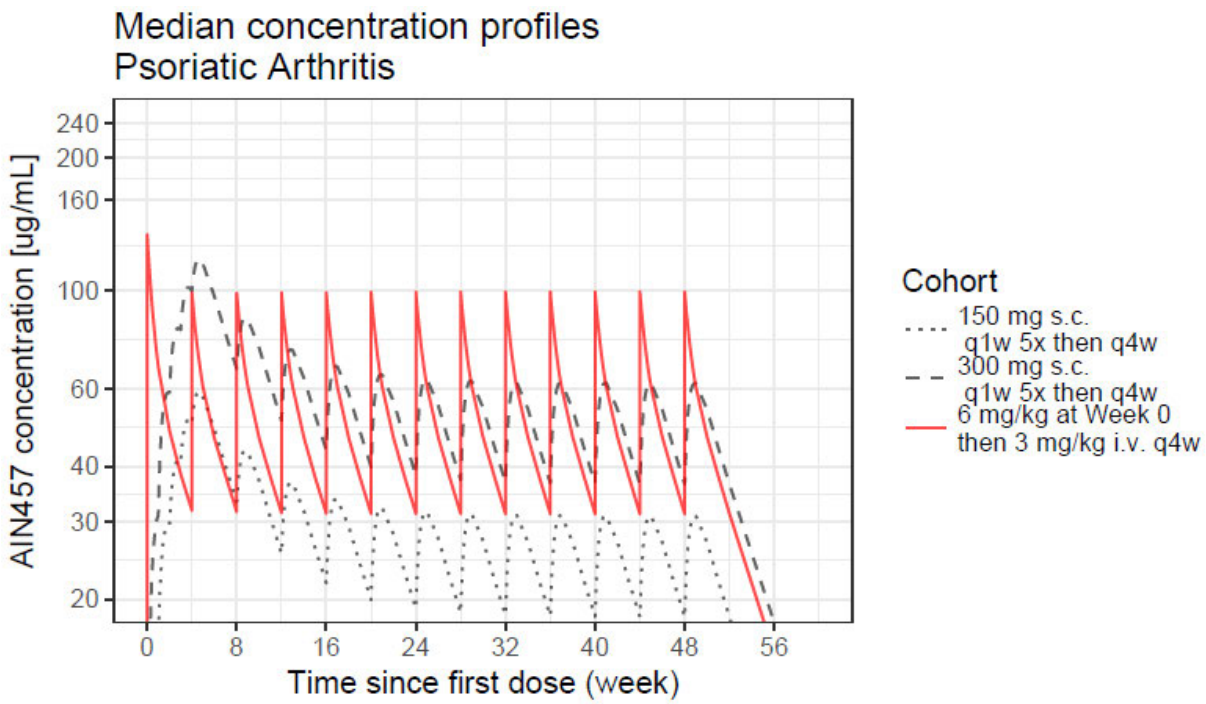
In addition, pertaining to safety assessments, there were no clinically meaningful differences among the secukinumab doses of 300 mg and 150 mg in the exposure adjusted incidence rates of the key risks over the entire treatment period in the phase III trials in PsA patients.

The overall safety data in the PsA population was consistent with prior extensive experience in psoriasis and show that secukinumab 300 mg and 150 mg are acceptable for chronic use in adult patients with active PsA. However, despite the demonstrated clinical efficacy with 150 mg s.c. and 300 mg s.c, the fixed dose nature of these posologies imposes constraints in certain patient populations. Towards overcoming these constraints and to offer a weight based posology with its attendant flexibility, a regimen of i.v. secukinumab is being developed. The proposed i.v. regimen of secukinumab - 6 mg/kg at BSL and 3 mg/kg every 4 weeks thereafter – is a result of extensive [redacted] analysis and modelling based on data with 150 mg s.c. and 300 mg s.c. secukinumab.

This i.v. regimen of secukinumab - 6 mg/kg at BSL and 3 mg/kg every 4 weeks thereafter - is modelled to target a C_{min} that is consistently above that achieved with 150 mg s.c. with a maximum plasma concentration (C_{max}) and average plasma concentration (C_{avg}) close to that achieved with 300 mg. s.c. as illustrated in Figure 4-1. Hence, the proposed i.v. regimen of secukinumab is expected to deliver an exposure that would approximate the 300 mg s.c.

Given the amount of data collected so far [redacted], it is expected that the clinical response with the proposed i.v. regimen will be similar with that observed with the s.c. regimen.

Figure 4-1 Median concentration profiles



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

A placebo arm is included in this study as a comparator up to the primary endpoint at Week 16. Due to the nature of the disease and the outcome measures used (ACR50 response criteria) a placebo arm is necessary to compare efficacy measurements. The maintenance of the placebo treatment up to the primary endpoint at Week 16 is supported from an ethical standpoint by precedent of multiple placebo-controlled trials in PsA. 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 including registration studies of s.c. secukinumab in PsA and is also in accordance with EMA guidelines (EMA 2009). 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 subjects who are experiencing worsening of disease in any of the treatment groups can exit the study at any time upon their own accord or based on the advice of the investigator.

4.4 Purpose and timing of interim analyses/design adaptations

The primary endpoint analysis (Week 16 analysis) will be performed after all subjects complete the Week 16 visit in order to support regulatory filing(s).

Subsequent to the primary endpoint analysis, additional analyses are planned for regulatory submission and/or publication purposes for longer-term assessments of efficacy and safety after subjects have completed Week 60.

Additional analyses may be performed to support health authority interactions, as necessary.

The investigators, site personnel and monitors will continue to remain blinded to the original treatment assignment groups until Week 60 analysis has been completed.

4.5 Risks and benefits

Secukinumab has shown either preliminary or confirmed efficacy in several inflammatory diseases including psoriasis, psoriatic arthritis and ankylosing spondylitis. 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 phase II/III PsA trials did not show additional safety concerns.

Secukinumab is generally safe and well-tolerated. The most frequently reported adverse events 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 mostly 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 ($<1.0\text{-}0.5 \times 10^9$/L) was uncommonly observed with secukinumab, most were transient and reversible without a temporal relationship to serious infections.

Hypersensitivity reactions, including urticarial and a 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 the i.v. regimen 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 subjects 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 Investigator's Brochure (IB). Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific stopping rules, are included in this protocol.

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

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

5 Population

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

Male and female subjects aged at minimum 18 years at time of consent, with active PsA fulfilling the CASPAR criteria (Refer to Appendix 16.2). Subjects 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 BSL (dactylitis of a digit in the foot or hand counts as one tender and swollen joint).

Subjects must have either signs of skin manifestations of plaque psoriasis or present nail changes consistent with psoriasis or a documented history of plaque psoriasis.

Subjects must report active disease despite current or previous NSAIDs, DMARDs and / or TNF inhibitor therapy or intolerance to these therapies. 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 randomization visit.

Subjects can be re-screened only once and no re- screening study related procedures should be performed prior to written re-consent by the subject. Mis-randomized subjects will not be re-screened.

This is an international study and it is expected that approximately 380 subjects will be enrolled.

A screening failure rate of 30% and post-randomization dropout rate of 10% is anticipated. Enrollment will stop as soon as the target number of randomized subjects is reached.

5.1 Inclusion criteria

Patients who are TNF-IR's (primary or secondary failure of efficacy, failure to tolerate or contraindication) are allowed to enter the study (up to 25% of patient numbers). Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Subject 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 subjects 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 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. RF and anti-CCP antibodies negative at screening.
5. Diagnosis of active plaque psoriasis or nail changes consistent with psoriasis or a documented history of plaque psoriasis.
6. Subjects with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs.
7. Subjects who are regularly taking NSAIDs and/or acetaminophen/paracetamol 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.
8. Subjects taking corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 16.
9. Subjects taking MTX (≤ 25 mg/week) are allowed to continue their medication if the dose and route of administration is stable for at least 4 weeks before randomization and should remain on a stable dose up to Week 16.
10. Subjects on MTX must be on folic acid supplementation at randomization.

11. Subjects who are on a conventional synthetic (CS) DMARD other than MTX must discontinue the DMARD 4 weeks prior to randomization visit except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed.
12. Subjects who have been on a TNF inhibitor must have experienced an inadequate response to previous or current treatment with a TNF inhibitor given at an approved dose for at least 3 months or have stopped treatment due to safety/tolerability problems after at least one administration of a TNF inhibitor.
13. Subjects who have previously been treated with TNF inhibitors (investigational or approved) will be allowed entry into study after appropriate wash-out period prior to randomization:
    - 4 weeks or longer for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route)
    - 8 weeks or longer for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (s.c. and i.v. infusion)
    - 10 weeks or longer for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route)
    - 10 weeks or longer for Simponi® (golimumab) – with a terminal half-life of 11-14 days (s.c. and i.v. infusion)
    - 10 weeks or longer for Cimzia® (certolizumab) – with a terminal half-life of approx. 14 days (s.c. route)

5.2 Exclusion criteria

Subjects 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 subjects.

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. Subjects taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine)
3. Ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, UV therapy) at randomization. The following wash-out periods need to be observed:
    a. Oral or topical retinoids- 4 weeks
    b. Photochemotherapy (e.g. PUVA)- 4 weeks
    c. Phototherapy (UVA or UVB)- 2 weeks
    d. Topical skin treatments (except in face, eyes, scalp and genital area during screening, only corticosteroids with mild to moderate potency)- 2 weeks
4. Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization.
5. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization.
6. Subjects who have previously been treated with more than 3 different TNF-a inhibitors (investigational or approved).

7. Subjects who have ever received biologic immunomodulating agents, investigational or approved except for those targeting TNFα.
8. 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 hCG laboratory test.
9. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the entire study or longer if required by locally approved prescribing information (e.g. 20 weeks in EU). Effective contraception is defined as either:

   a.Barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicide (where available). Spermicides alone are not a barrier method of contraception and should not be used alone.

   The following methods are considered more effective than the barrier method and are also acceptable:

   a.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].

   b.Female sterilization: have had a 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.

   c.Use of established oral, injected or implanted hormonal methods of contraception, intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral contraception women should have been stable on the same pill for a minimum of 12 weeks before taking study treatment.

   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 the Central Lab FSH and/or estradiol levels.
10. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy such as inflammatory bowel disease (IBD).
11. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the subject and/or places the subject at unacceptable risk for participation in an immunomodulatory therapy.
12. 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.
13. 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 may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out lab error

b. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 µmol/L)

14. History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6µmol/L)
15. Screening total WBC count <3,000/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL (85g/L)
16. Active systemic infections during the last two weeks (exception: common cold) prior to randomization
17. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive 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 TB-Gold test as indicated in the assessment schedule. Subjects with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.
18. Known infection with HIV, hepatitis B or hepatitis C at screening or randomization.
19. 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).
20. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the subject unsuitable for the trial.
21. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
22. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
23. Donation or loss of 400 mL or more of blood within 8 weeks before randomization.
24. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization.
25. Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization.
26. Use of other investigational drugs at the time of enrollment, or within 5 half- lives of enrollment, or within 4 weeks until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations.
27. History of hypersensitivity to any of the study drug constituents.
28. Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor.

29. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19).

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Novartis will supply the following study treatments:

Investigational Treatment:

- Secukinumab liquid in vial (LiV) for i.v. infusion provided in glass vials, each containing 125 mg / 5 mL secukinumab Concentrate for solution for infusion

Reference Therapy:

- Secukinumab placebo Concentrate for solution for i.v. infusion provided in 5 mL LiV

The LiV glass vials are packed in double-blind (treatment period 1, up to and including Week 12) and open label fashion (treatment period 2, from Week 16 onwards). For detailed instructions for storage, handling and administration of study treatment, please refer to the Pharmacist Manual.

The study medication will be labeled as follows:

- Double-blind Secukinumab Liquid in Vial will be labeled as AIN457 125 mg/5 ml/ Placebo.
- Open-label Secukinumab Liquid in Vial will be labeled as AIN457 125 mg/5 ml.

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

At baseline, eligible subjects will be randomized to one of the following two treatment arms in a 1:1 ratio (see Figure 3-1).

Group 1: secukinumab i.v. (6 mg/kg) at BSL, followed by secukinumab 3 mg/kg i.v. every four weeks starting at Week 4 through Week 48 (exposure through week 52).

Group 2: placebo i.v. at BSL, Week 4, 8 and 12 followed by secukinumab 3 mg/kg i.v. every four weeks starting at Week 16 through Week 48 (exposure through week 52).

6.1.4 Treatment duration

The planned duration of treatment is 52 weeks. Subjects may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the subject.

6.2 Other treatment(s)

No additional treatment beyond investigational drug is provided in this trial.

6.2.1 Concomitant therapy

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

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

Guidelines for the use of specific medications are provided below.

Methotrexate (MTX)

Subjects taking MTX (up to 25 mg/week) must be on a stable dose for at least 4 weeks before randomization and maintained stable until Week 16.

Leflunomide wash-out with cholestyramine

In case of leflunomide treatment before study randomization, a drug wash-out of 8 weeks must be performed. However, another wash-out procedure can be considered. Cholestyramine may be given orally at a dose of 8 g three times daily (t.i.d) to wash-out leflunomide. Cholestyramine 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 subjects who require a drug elimination procedure. If a subject receives 8 g t.i.d. for 11 days, the subject can 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 if the dose was 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.

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

Intra-articular corticosteroids are not permitted within 4 weeks prior to baseline and up to Week 16. After Week 16, no more than 1 joint per 24-week period may be injected. No single injection should exceed 40 mg of triamcinolone (or equivalent) and the total dose of intra-articular corticosteroid may not exceed 80 mg of triamcinolone (or equivalent) during any 52-week period. Injection of intra-articular corticosteroids is not permitted within 8 weeks prior to Week 52. The joints injected with intra-articular corticosteroids will be assessed as both swollen and tender in the SJC and TJC, from injection time onwards.

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

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

Subjects taking NSAIDs, low strength opioids or paracetamol/acetaminophen PRN within the 2 weeks before randomization can continue to do so in the study; however, they have to refrain from any intake during at least 24 hours before a visit with disease activity assessment. Regular dosing with low strength opioids is not permitted.

After the Week 16 assessments are completed, a change in the NSAID intake regimen is permitted.

Any change of the NSAID/paracetamol/acetaminophen treatment during the trial should be recorded on the corresponding eCRF page.

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-1 is NOT allowed after the start of the washout period unless specified otherwise below.

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

Table 6-1 Prohibited medication

Medication	**Washout period (before randomization)**	**Action (after randomization)**
Any biologic drugs, including but not limited to TNFα inhibitors, secukinumab, or other biologic drugs targeting IL-17 or IL-17 receptor • Etanercept • Infliximab • Adalimumab, golimumab, certolizumab	Biological immunomodulating agents > 3 different TNFα Inhibitors: never • 4 weeks • 8 weeks • 10 weeks	Discontinue investigational treatment
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents [e.g., alemtuzumab (Campath), anti-CD4, anti-CD5, anti-CD3, and anti-CD19]	Never	Discontinue investigational treatment
Conventional synthetic DMARDs (with the exception of MTX) and ts-DMARDs including apremilast, tofacitinib etc	4 weeks	Discontinue investigational treatment
Leflunomide	8 weeks	Discontinue investigational treatment
Leflunomide with cholestyramine washout	4 weeks	Discontinue investigational treatment

Medication	**Washout period (before randomization)**	**Action (after randomization)**
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)	Discontinue investigational treatment
Unstable dose of NSAIDs (including selective COX-2 inhibitors)	2 weeks	Discontinue investigational treatment. (Dose adjustments allowed after week 16) Discontinuation of investigational treatment may be required on a case by case basis.
Analgesics other than NSAIDs, paracetamol/acetaminophen, and low strength opioids PRN +	2 weeks	Discontinue investigational treatment
Systemic corticosteroids > 10 mg prednisone equivalent (until Week 16)*	2 weeks	If administered due to a medical urgency unrelated to the patient's arthritis, study treatment should be interrupted until the steroid is discontinued. If not administered for a medical urgency or for use related to the patient's arthritis, then discontinuation of investigational treatment may be required on a case by case basis
Unstable dose of systemic corticosteroids ≤ 10 mg prednisone equivalent (until Week 16)*	2 weeks	Discontinue investigational treatment (Dose adjustments allowed after week 16) Discontinuation of investigational treatment may be required on a case by case basis.
Intra-articular corticosteroids injections, (until Week 16)*	4 weeks	Discontinue investigational treatment
Intramuscular or intravenous corticosteroid treatment	4 weeks	Discontinuation of investigational treatment may be required on a case by case basis
Live vaccinations	6 weeks	If administered due to a medical urgency, study treatment should be interrupted for 4 months. If administered not for a medical urgency then discontinue investigational treatment
Oral or topical retinoids	4 weeks	Discontinue investigational treatment
Photochemotherapy (e.g. PUVA)	4 weeks	Discontinue investigational treatment

Medication	Washout period (before randomization)	Action (after randomization)
Phototherapy (UVA or UVB)	2 weeks	Discontinue investigational treatment
Topical skin treatments (except in face, eyes, scalp and genital area; only corticosteroids with mild to moderate potency)	2 weeks	Discontinue investigational treatment

* see details about corticosteroid management in Section 6.2.1.
+ Regular dosing with low strength opioids is not permitted.

6.2.3 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. Although no subject will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if rescue with prohibited biologics (as described in Section 6.2.2) occurs prior to completion of Week 16 assessments, subjects will be discontinued from study treatment. Subjects who are deemed not to be benefiting from the study treatment based upon safety and efficacy assessments by the investigator or for any reason on their own accord will be free to discontinue participation in the study at any time.

Changes in NSAIDs concomitant therapy is permitted after Week 16 assessments as per investigator's clinical judgment. After Week 16, the dose and regimen of other concomitant medications may be adjusted slowly at the investigator's discretion and recorded appropriately on the CRF page.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.) that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Once assigned to a subject, the Subject No. will not be reused. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

At BSL, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. 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 arm 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 subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supplies using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The subjects will be stratified at randomization according to either TNF -IR or TNF- naïve subjects. Up to 25% of randomized subjects will be TNF- IR to ensure a representative subject population for the assessment of efficacy and safety.

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

6.4 Treatment blinding

This is a double-blind, randomized treatment trial.

Subjects, investigator staff, persons performing the assessments will remain blinded to the identity of the treatment from the time of randomization until Week 60 database lock, using the following methods:

(1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the exception of the bioanalyst.

(2) The identity of the treatments will be concealed by the use of study treatments in the form of i.v. injection, filled with secukinumab or placebo that are identical in appearance.

[redacted]

As the primary analysis will be performed at Week 16, there will be a database lock when all subjects have completed Week 16 assessments. Summary results may be shared internally and externally, however individual unblinded subject data will not be disclosed at this time. For details regarding the planned Interim Analyses, refer to Section 12.7.

A final database lock will occur when all subjects have completed the study. After the Week 60 analysis has been conducted, the Novartis clinical team will notify the investigative staff and the IRT system and site personnel and the subject will be unblinded to the originally assigned treatment arms.

Starting at the Week 16 visit, all subjects initially randomized to placebo will be receiving the secukinumab however, unblinding of the original randomization before Week 60 database lock will only occur in the case of subject emergencies (see Section 6.6.3)

The high sensitivity C-reactive protein (hsCRP) results from samples collected during the treatment period will be revealed only after database lock and analyses are completed.

6.5 Dose escalation and dose modification

No study treatment dose escalations and/or adjustments are permitted.

6.5.1 Dose modifications

Temporary interruptions (e.g., in case of ongoing AE, surgical procedure at based of treating physician's discretion) of study medication are permitted. Study medication should be reintroduced under careful monitoring if the investigator feels if it is in the best interest of the subject. These dose interruptions must be recorded on the appropriate CRF.

6.5.2 Follow-up for toxicities

Subjects whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant abnormal laboratory value, must be followed up in accordance with what is clinically indicated per the investigator until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrist, etc., should be consulted as deemed necessary.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

All dates and times of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page.

Drugs administered prior to start of treatment and other drugs/procedures continuing or started during the study treatment period will be entered in the Prior/Concomitant medications or Significant non-drug therapies eCRF page.

Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons as described in Section 6.5.2 . Compliance will also be assessed by a Novartis monitor using information provided by the authorized site personnel.

6.6.2 Recommended treatment of adverse events

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment 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 monitor for the site and the study team that the code has been broken.

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

- protocol number
- study drug name
- subject number

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

Study drug must be discontinued after emergency unblinding.

6.7 Preparation and dispensation

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

A unique medication number is printed on the study medication label.

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

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug

accountability log to the Novartis monitor or to the Novartis/address provided in the investigator folder at each site.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

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

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

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

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

Subjects will be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. **The study treatment should not be administered within less than 14 days after the previous administration.**

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for an end of treatment visit 4 weeks after the last study treatment. At this visit, all of the assessments listed for the final visit will be performed (correspond to the last visit for the subject's current period of treatment (treatment period 1 or 2): i.e., Week 16 or Week 52). At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF. A follow-up visit is to be done 8 weeks after the end of treatment visit, for all subjects, regardless of whether they complete the entire study as planned or discontinue prematurely

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

Table 8-1 Assessment Schedule

Period	Screening[2]		Treatment Period 1					Treatment Period 2										Follow-up
Visit Name	Screening visit 1 (-10 to -4 BSL)	Screening visit 2 (≤ -4 to BSL)	Baseline	Week 4	Week 8	Week 12	Week 16	week 20	week 24	Week 25	Week 28	week 32	week 36	Week 40	Week 44	Week 48	Week 52	Week 60
Visit Numbers[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Informed consent	X																	
Inclusion / Exclusion criteria	X	X	X															
Hepatitis and HIV Screen[3,4]	S																	
Relevant medical history/ current medical condition	X	X																
Washout evaluation/ instructions	S																	
Smoking history	X																	
Cardiovascular medical history	X																	
Demography	X																	
Psoriasis/psoriatic arthritis medical history and previous therapies	X																	
PsA CASPAR Criteria		X																
Physical Examination		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S

Period	Screening[2]		Treatment Period 1					Treatment Period 2										Follow-up
Visit Name	Screening visit 1 (-10 to -4 BSL)	Screening visit 2 (≤ -4 to BSL)	Baseline	Week 4	Week 8	Week 12	Week 16	week 20	week 24	Week 25	Week 28	week 32	week 36	Week 40	Week 44	Week 48	Week 52	Week 60
Visit Numbers[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Body Height		X																
Body Weight		X	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray/ MRI[5,6]		S																
Electrocardiogram (ECG)	S																	
Randomization via IRT			X															
PPD skin test or QuantiFERON TB-Gold Test[7]		X																
Administration of study treatment via I.V. at study site			X	X	X	X	X	X	X		X	X	X	X	X	X		
Prior/Concomitant medication/ non-drug therapy	X	Update as necessary																
Adverse events/ SAEs (incl. injection site reaction & occurrence of infections)[8]	X	Update as necessary																
Hematology		X	X	X	X	X	X		X		X			X			X	X
Clinical Chemistry		X	X	X	X	X	X		X		X			X			X	X
Lipid profile[9]			X		X		X		X								X	
Urinalysis			X		X		X		X								X	

Period	Screening[2]		Treatment Period 1					Treatment Period 2										Follow-up
Visit Name	Screening visit 1 (-10 to -4 BSL)	Screening visit 2 (≤ -4 to BSL)	Baseline	Week 4	Week 8	Week 12	Week 16	week 20	week 24	Week 25	Week 28	week 32	week 36	Week 40	Week 44	Week 48	Week 52	Week 60
Visit Numbers[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Cardiovascular panel			X				X		X								X	
Serum pregnancy test		X																
Urine pregnancy test [11]			S	S	S	S	S	S	S		S	S	S	S	S	S	S	S
Anti-CCP	X																	
Rheumatoid factor (RF)	X																	
Erythrocyte sedimentation rate[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
High sensitivity C Reactive protein (hsCRP)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tender and swollen joint counts (TJC78, SJC76)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's assessment of PsA pain intensity (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	Screening[2]		Treatment Period 1					Treatment Period 2										Follow-up
Visit Name	Screening visit 1 (-10 to -4 BSL)	Screening visit 2 (≤ -4 to BSL)	Baseline	Week 4	Week 8	Week 12	Week 16	week 20	week 24	Week 25	Week 28	week 32	week 36	Week 40	Week 44	Week 48	Week 52	Week 60
Visit Numbers[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Patient's global assessment of disease activity (VAS)			X	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	X
[redacted]																		
Health Assessment Questionnaire-Disability Index (HAQ-DI)			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	X	
Leeds Dactylitis Index (LDI)			X	X	X	X	X		X	X		X		X		X	X	
Leeds Enthesitis Index (LEI)			X	X	X	X	X		X	X		X		X		X	X	
[redacted]																		
PASI			X	X	X	X	X		X	X		X		X		X	X	
[redacted]																		

Period	Screening[2]		Treatment Period 1					Treatment Period 2										Follow-up
Visit Name	Screening visit 1 (-10 to -4 BSL)	Screening visit 2 (≤ -4 to BSL)	Baseline	Week 4	Week 8	Week 12	Week 16	week 20	week 24	Week 25	Week 28	week 32	week 36	Week 40	Week 44	Week 48	Week 52	Week 60
Visit Numbers[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
mNAPSI (only in subjects with nail involvement of hands)			X	X	X	X	X		X	X		X		X			X	
Physician's global assessment of fingernail disease severity (VAS)			X	X	X	X	X		X	X		X		X			X	
SF-36 v2			X	X	X	X	X		X		X						X	
FACIT-Fatigue v4			X	X	X	X	X		X		X						X	
[redacted]																		
Trial feedback Questionnaire (TFQ)			X								X							X
Treatment period 1 completion form							X											
Treatment period 2 completion form																	X	
Follow-up period completion form																		X

Period	Screening[2]		Treatment Period 1					Treatment Period 2										Follow-up
Visit Name	Screening visit 1 (-10 to -4 BSL)	Screening visit 2 (≤ -4 to BSL)	Baseline	Week 4	Week 8	Week 12	Week 16	week 20	week 24	Week 25	Week 28	week 32	week 36	Week 40	Week 44	Week 48	Week 52	Week 60
Visit Numbers[1]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] If the subject's washout period ≤ 4 weeks, Screening visit 1 (SV1) and Screening visit 2 (SV2) can be performed on the same day.
[3] These assessments are source documentation only and will not be entered into the eCRF. However, data regarding to which inclusion/exclusion criteria are not met are captured on the Inclusion/Exclusion eCRF.
[4] Hepatitis B and/or hepatitis C and/or HIV serology testing to be performed during screening period only if required as per local medical practice or local regulations prior to initiation of therapy. These assessments will be documented in source records only and will not be entered into the eCRF.
[5] A chest x-ray or MRI is required if it was not performed and evaluated within 3 months prior to screening. The x-ray should be performed after it is certain the subject meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation. The x-ray may be replaced by an MRI assessment.
[6] A copy of the x-ray or radiologist's report must be kept in the source documentation.
[7] The PPD skin test can be performed at any time during the screening period, but it must be read within 72 hours and before randomization.
[8] AEs / SAEs occurring after the subject has signed the informed consent must be captured on the appropriate eCRF page.
[9] Sample must be obtained fasting.
[redacted]
[11] Kits will be provided by central lab and test is to be performed locally.
[redacted]

8.1 Screening

Screening will consist of two visits and will be flexible in duration (4-10 weeks), based on the time required to washout prior anti-rheumatic medications, during which time the subject will sign the ICF, be evaluated for eligibility and have sufficient time for potential medication washout, in addition to all other assessments indicated in Table 8-1.

During the first screening visit, initial assessments will be performed as outlined in Table 8-1. At that visit the duration of the washout period will be determined. The second screening visit will be performed as follows:

- If the washout period is ≤ 4 weeks the investigator should proceed directly to visit 2 on the same day and complete all assessments
- If the washout period is more than 4 weeks, the subject will be instructed to initiate necessary washout regimen, and return for Visit 2 within 4 weeks of the target randomization date (i.e., in all cases, Visit 2 should not happen earlier than 4 weeks prior to randomization.

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

All subjects 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.

8.1.1 Information to be collected on screening failures

Subjects who discontinue from the study prior to randomization are considered screening failures.

If a subject discontinues before entering the double-blind treatment period at BSL, IRT must be notified within 2 days and the reason for not being randomized will be entered on the appropriate eCRF page. 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.

All subjects who have signed informed consent and are randomized into the double-blind treatment period at BSL will have all adverse events **occurring after informed consent is signed** recorded on the Adverse Event CRF.

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

8.2 Subject demographics/other baseline characteristics

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

- Age, sex, race, ethnicity and source of subject referral
- Relevant PsA/Psoriasis and general medical history/current medical condition data until the start of study treatment, such as date of diagnosis of PsA/Psoriasis, previous PsA/Psoriasis therapies with the status of prior TNFα inhibitor use, cardiovascular medical history, and smoking history

Whenever possible, diagnoses and not symptoms will be recorded.

8.3 Efficacy

The efficacy outcome measures used in this study are the standard measures used across all PsA trials and required for filing. All efficacy assessments should be performed prior to administration of study treatment.

- American College of Rheumatology (ACR) 20, 50 and 70 responses
- Swollen Joint Count (SJC)/Tender Joint Count (TJC)
- Patient's global assessment of disease activity (VAS)
- Physician's global assessment of disease activity (VAS)
- Patient's assessment of PsA pain intensity (VAS)
- Health Assessment Questionnaire – Disability Index (HAQ-DI©)
- [redacted]
- High sensitivity C-Reactive Protein (hsCRP)
- Erythrocyte Sedimentation Rate (ESR)
- [redacted]
- [redacted]
- Psoriatic Arthritis Disease Activity Score (PASDAS)
- Patient's global assessment of psoriasis and arthritis disease activity (VAS)
- Minimal disease activity
- Leeds Dactylitis Index (LDI) and dactylitis count
- Leeds Enthesitis Index (LEI)
- [redacted]
- Psoriasis Area and Severity Index (PASI)
- [redacted]
- Modified Nail Psoriasis Severity Index (mNAPSI)
- Physician global fingernail disease severity assessment (VAS)
- [redacted]

Patient reported outcomes (PROs) will be collected using the ediary technology.

The subject should must be given the PRO measure(s) to be completed at the scheduled visit before any clinical assessments are conducted

Details relating to the administration of all PROs are provided in Appendix 16.12.

8.3.1 American College of Rheumatology (ACR) response

The ACR response (Appendix 16.4) will be used to determine efficacy (Felson et al 1995). A subject is defined as an ACR 50 responder if, and only if, the following three conditions hold:

≥ 50% improvement in the number of tender joints (based on 78 joints)

≥ 50% improvement in the number of swollen joints (based on 76 joints)

≥ 50% improvement in three of the following five measures:

- 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- Disability Index (HAQ-DI©) score
- Acute phase reactant (hsCRP or ESR)

ACR20 = 20 % improvement in at least 3 of the 5 measures and 20 % improvement in the swollen and tender joint count.

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

[redacted]

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

8.3.2 Tender 78 joint count and swollen 76 joint count

Joint counts will be performed by the independent assessor(s) who must be well trained and part of the site personnel. Whenever possible, the same evaluator should perform these assessments at all visits (Refer to Appendix 16.4 for more details).

During the open label phase of the study, as much as 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 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 all 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.

8.3.3 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*".

8.3.4 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.

8.3.5 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*".

8.3.6 Health Assessment Questionnaire - Disability Index (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 subjects with PsA.

Refer to Table 8-1 and Appendix 16.9 for more details.

[redacted]

8.3.8 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.

8.3.9 Erythrocyte sedimentation rate (ESR)

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

[redacted]

8.3.11 Psoriatic Arthritis Disease Activity Score (PASDAS)

PASDAS is a new composite measure developed to access disease activity in Psoriasis (GRACE Project) (Helliwell et al, 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), enthesitis (LEI), 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 x LN (Dactylitis count + 1))

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

8.3.11.1 VAS for PASDAS (Psoriatic Arthritis Disease Activity Score) assessment

Please indicate with a vertical mark (|) through the horizontal line your answer to the following question relating to the past week.

In all the ways in which your PSORIASIS and ARTHRITIS, as a whole, affects you, how would you rate the way you feel over the past week?

[redacted]

8.3.13 Minimal disease activity

The proportion of subjects achieving minimal disease activity (MDA) (Coates et al 2010) is assessed as 5 of the 7 following: ≤ 1 tender joint count, ≤ 1 swollen joint count, PASI ≤ 1 or BSA≤3%, patient pain VAS ≤ 15, patient global assessment of disease activity VAS ≤ 20, HAQ-DI© ≤ 0.5, tender entheseal points ≤ 1).

8.3.14 Leeds Dactylitis Index (LDI)

The Leeds Dactylitis Index (LDI) (Helliwell et al 2005) basic measures the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot, using a minimum difference of 10% to define a dactylitic digit. The ratio of circumference is multiplied by a tenderness score, using a modification of LDI that is a binary score (1 for tender, 0 for non-tender). If both sides are considered involved, or the circumference of the contralateral digit cannot be obtained, the number will be compared to data provided in the standard reference tables (see Appendix 16.8 and Table 8-1). This modification is referred to as LDI basic and will be applied in this study. The LDI requires a finger circumference gauge or a dactylometer to measure digital circumference.

Dactylitis count

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

Presence of dactylitis

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

8.3.15 Leeds Enthesitis Index (LEI)

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

Presence of enthesitis

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

8.3.16 Psoriasis Area and Severity Index (PASI)

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 et al 2003) will be derived as indicated in Table 8-2.

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

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

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

Table 8-2 The PASI scoring system

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

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

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

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

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

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

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

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

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

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0. The investigator is responsible for collecting the components or scoring signs and total regional area. More information is provided in Table 8-1 and Appendix 16.6.

8.3.18 Modified Nail Psoriasis Severity Index (mNAPSI)

The mNAPSI is an instrument to assess psoriatic nail involvement in subjects with PsA and nail psoriasis. It will be collected only in subjects with psoriatic nail involvement. The modifications on the original NAPSI to create the mNAPSI were made by rheumatologists, with dermatologists' input, as a tool for clinical trials. The creators' goal was to develop a tool to assess disease severity and response to treatment in clinical trials, keeping in mind that the assessor in a clinical trial most likely would not be a trained dermatologist (Cassell et al 2007). Detailed information is provided in Appendix 16.7.

For the evaluation of the mNAPSI three features or groups of features (onycholysis and oil-drop dyschromia, pitting and crumbling) of each fingernail will be graded on a scale from 0 to 3:

- Onycholysis: Separation of the nail plate from the nail bed. The separated part of the nail is opaque and can have white, yellow, or greenish tinge. If there is a piece of nail missing, estimate where the nail normally would have ended at the end of the nail bed, and count that missing part as involved in onycholysis.
- Oil-drop (salmon patch) dyschromia: Reddish-brown discoloration under the nail plate.

Onycholysis and oil-drop dyschromia are considered together. When looking at the nail, combine the total percentage area of the nail that is affected by either and use that combined total to score the nail.

Table 8-4 Score for percent of nail with onycholysis or oil-drop dyschromia

Score	Percent of nail with onycholysis or oil-drop dyschromia present
0	No onycholysis or oil drop dyschromia present
1	1–10% of the nail has onycholysis or oil-drop dyschromia
2	11–30% of the nail has onycholysis or oil-drop dyschromia
3	> 30% of the nail has onycholysis or oil-drop dyschromia

- Pitting: Small, sharply defined depressions in the nail surface. Pits are discrete abnormalities ("ice-pick-like"). If there is nail plate crumbling that is confluent with pits, do not score for pits. If the pits are separate from crumbling, they may be scored regardless of whether crumbling is present or not.

Table 8-5 Score for number of pits

Score	Number of pits
0	0
1	1–10
2	11–49
3	> 50

- Nail plate crumbling: Crumbling or fragmentation of friable nail plate which may be associated with confluent pitting. Crumbling involves alteration of the nail plate surface. Horizontal ridging of the nail, "wave-like" appearance, and horizontal lines are all features of crumbling.

Table 8-6 Score for percent of nail with crumbling present

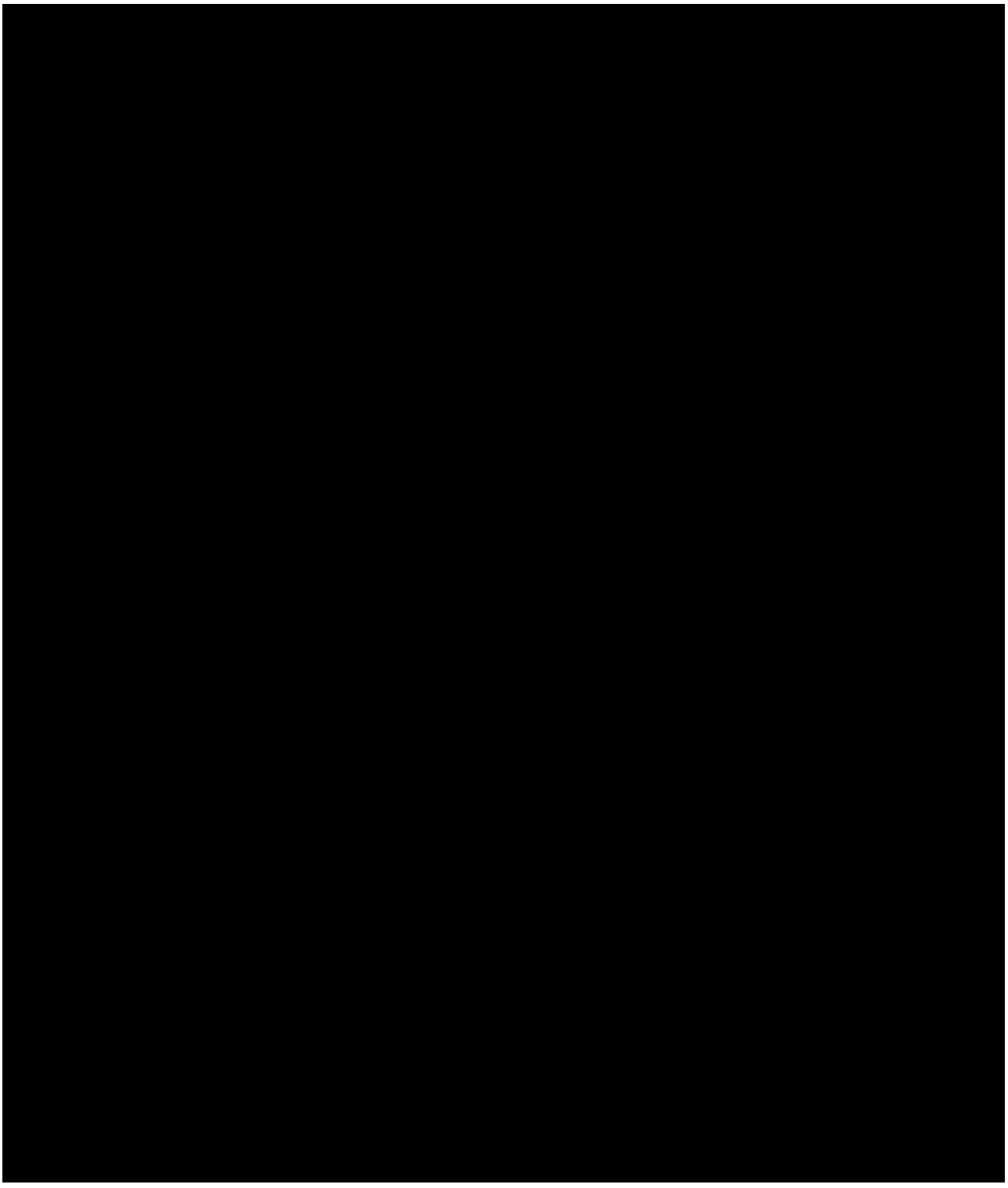
Score	Percent of nail with crumbling present
0	No crumbling
1	1–25% of the nail has crumbling
2	26–50% of the nail has crumbling
3	> 50% of the nail has crumbling

The next 4 abnormalities (leukonychia, splinter hemorrhages, hyperkeratosis, and red spots in the lunula) are scored only as either present or absent for each fingernail. A score of 1 indicates present and a score of zero indicates not present.

1. Leukonychia: White spots in the nail plate due to psoriasis in the mid matrix. Leukonychia are just color changes. If it appears that there is depression or irregularity to the nail surface, this may be pitting or crumbling, not leukonychia. If the leukonychia is adjacent to or confluent with crumbling or pits, it is counted as part of the crumbling or pitting and not as a separate abnormality.
2. Splinter hemorrhages: Small, longitudinal, linear, dark brown hemorrhage under the fingernail.
3. Nail bed hyperkeratosis: Thickened keratin in the nail bed.
4. Red spots in the lunula: Small pink or red macules in the lunula.

8.3.19 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]

8.4 Safety

Evaluation of all AEs and SAEs including injection site reactions, electrocardiograms (ECGs), physical examination, vital signs and laboratory assessments will occur. [redacted]

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, Lipid Panel, Urinalysis, cardiovascular panel)
- Pregnancy and assessment of fertility
- Tolerability of secukinumab

[redacted]

Table 8-8 Assessments & Specifications

Assessment	Specification
Physical examination	A physical examination of the subjects will be performed according to the schedule defined in Table 8-1. A complete physical examination will include the examination of general appearance, hydration status, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

	Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent form must be recorded on the appropriate CRF that captures medical history screen on the CRF. Significant findings that occur after signing informed consent form which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs will include blood pressure and pulse rate measurements after 5 minutes rest in sitting position. If possible, vital signs assessments should be performed by the same study site staff member using the same validated device throughout the study.
Height and weight	Height in centimeters (cm) and body weight, to the nearest 0.1 kilogram (kg), in indoor clothing but without shoes, will be measured. If possible, body weight assessments should be performed by the same study site staff member using the same scale throughout the study.

QuantiFERON TB-Gold test or PPD skin test

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

QuantiFERON TB-Gold test

A QuantiFERON TB-Gold test is to be performed at the second SCR visit and the results to be known prior to randomization to determine the subject's eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection.

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

PPD skin test

A PPD skin test is to be performed at screening and read before randomization to determine the subject's eligibility for the trial, if a QuantiFERON test is not performed. The test dose is bioequivalent to 5 tuberculin units of standard PPD injected intradermally, usually into the volar surface of the forearm. The site is cleaned and the PPD extract is then injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration), will take 48-72 hours to develop, the subjects must return to the study site within that time for evaluation of the injection site. This will determine whether

the subject has had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration ≥5 mm (or according to local practice/guidelines) is interpreted as a positive result.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed below (except urinalysis). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. For the identification of clinically notable values, see Appendix 16.1 . All subjects 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.

Table 8-9 Specifications of Laboratory evaluations

Test Category	Test Name
Hematology	Hemoglobin, platelets, red blood cell (RBC), white blood cell (WBC) and differential white blood cell counts will be measured at scheduled visits.
Clinical Chemistry	Serum chemistries will include glucose, urea, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorus, total protein, albumin, and uric acid.
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.
Lipid Panel	A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), total cholesterol, and triglycerides will be measured from a fasting blood sample.
Cardiovascular Panel	A cardiovascular profile including lipoprotein (a), apolipoprotein B, apolipoprotein A-1, and adiponectin will be measured from a blood sample.
Pregnancy Test	Serum / Urine pregnancy test (Refer to Section 8.4.3)

8.4.2 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed as indicated in Table 8-1. 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 followed by vital signs and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety

concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings must be discussed with the sponsor before administration of investigational treatment.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF as appropriate.

8.4.3 Pregnancy and assessments of fertility

The study treatment must not be given to pregnant women; therefore, effective methods of birth control must be used for women of childbearing potential (see exclusion criteria definitions, Section 5.2).

A serum β-hCG test will be performed in all women at screening. All women who are not surgically sterile or post-menopausal (as defined in Section 5.2) at screening, will have local urine pregnancy tests as indicated in Table 8-1. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the subject must discontinue study treatment.

8.4.4 Other safety evaluations

Chest X-ray

Standard chest X-ray (PA view) will be performed except for those who have had a valid chest X-ray or MRI done within 3 months of first dosing.

8.5 Additional assessments

The other assessments planned for the study are:

- Quality of Life questionnaires/ Patient reported outcomes (PROs)

[redacted]

8.5.1 Clinical Outcome Assessments (COAs)

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

[redacted]

[redacted]

8.5.1.3 FACIT-Fatigue v4

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

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

[redacted]

8.5.1.5 Trial feedback Questionnaire (TFQ)

This trial will include an anonymized questionnaire, 'Trial Feedback Questionnaire' for subjects to provide feedback on their clinical trial experience. Individual subject level responses will not be reviewed by investigators. Responses would be used by the sponsor (Novartis) to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the subject's disease, symptoms, treatment effect or adverse events

and therefore would not be trial data. Should any spontaneous information be collected about AEs, this would be transferred to the safety database.

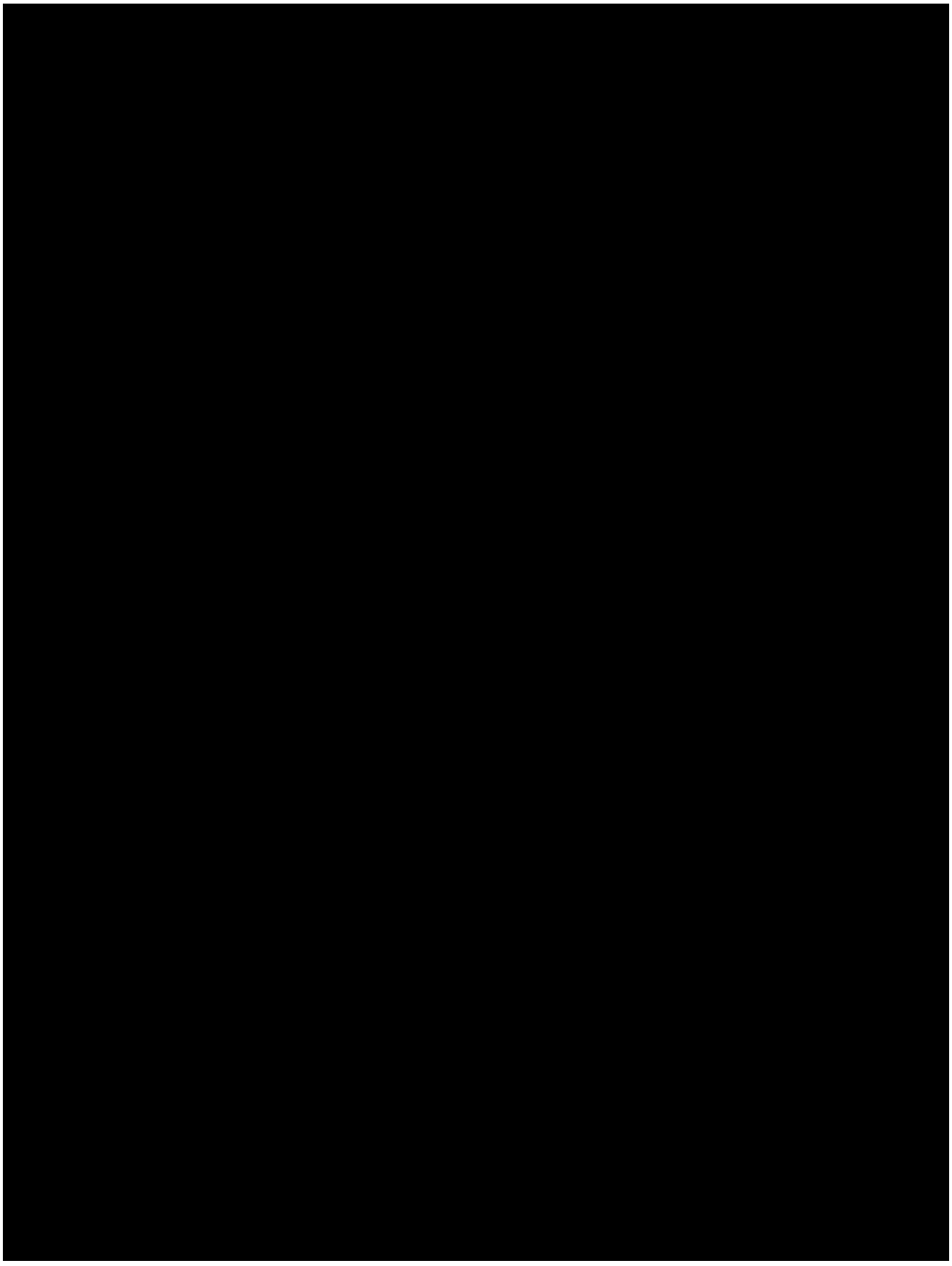
[redacted]

8.5.1.7 SF-36 v2

The SF-36 is a widely used and extensively studied instrument to measure health-related quality of life among healthy subjects and subjects with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed. The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual subjects.

The purpose of the SF-36 version 2, in this study is to assess the HRQoL (Health-related quality of life) of subjects. Given the chronic nature of this disease, recall period of 1 week will be used in this study as outlined in the assessment schedule (Table 8-1).

[redacted]



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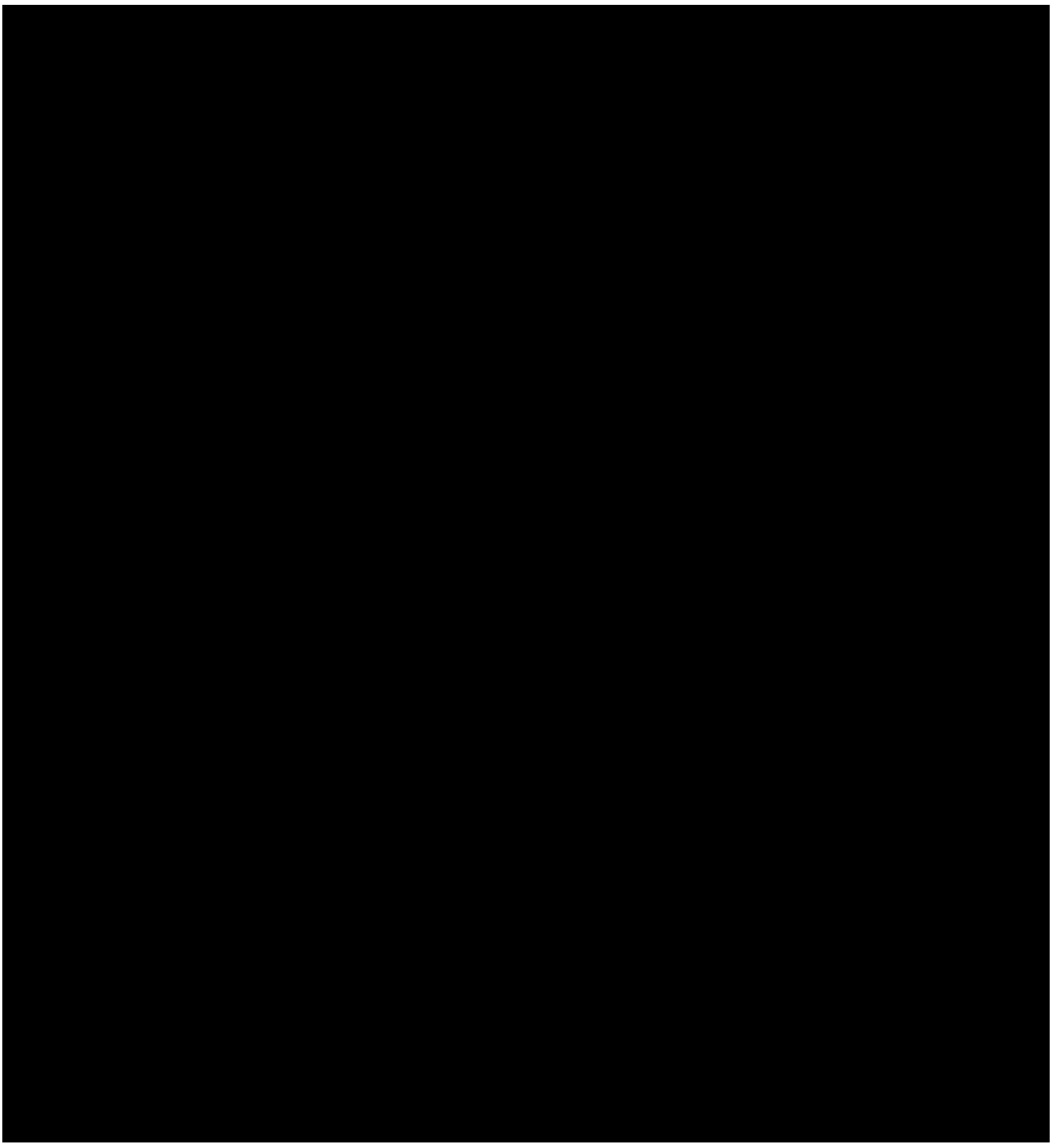


9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

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

  d. Severe hypersensitivity reaction or anaphylactic reaction
- Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the 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
- 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.

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

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' section). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

Subjects who prematurely discontinue or withdraw during a specific treatment period (i.e., Week 16 for treatment period 1 or Week 52 for treatment period 2) should return to site 4 weeks after the last study treatment for the final visit within that treatment period. Subjects should also return for the follow-up visit (Week 60) 12 weeks after the last study treatment (see Table 8-1). The final visit should be performed before any new treatment is initiated.

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section. Refer to Section 6.6.3.

9.1.2 Withdrawal of informed consent

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

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

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

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

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

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

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

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by

documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc.

A subject should not be formally considered lost to follow-up until due diligence has been completed or his/her scheduled End of Study visit would have occurred.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

A subject will be considered to have completed the study if he/she received a total of 52 weeks of study treatment and upon completion of the scheduled study assessments and procedures up to and including Week 60.

Information on the subject's completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the appropriate Study Phase Completion eCRF page.

In any case, the investigator or site staff must contact the IRT as soon as possible to record the subject's study completion (Week 60) and/or discontinuation.

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study as deemed appropriate by the investigator. This treatment may be any non-biologic DMARD. In case of a biologic treatment, a waiting period of 3 months before initiating the treatment is recommended.

If, at study completion, the investigator determines that a subject could benefit from continued secukinumab treatment, the physician may request access from Novartis, at no cost to the subject, if not commercially available and accessible.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. 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 investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

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

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

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

1. The severity grade

   mild: usually transient in nature and generally not interfering with normal activities

   moderate: sufficiently discomforting to interfere with normal activities

   severe: prevents normal activities
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/withdrawn
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Conditions that were already present after signing the informed consent should be recorded in medical history of the subject.

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

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

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

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

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 must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease.

10.1.2 Serious adverse events

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 seriousness criteria:

1. fatal
2. life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly/birth defect
5. requires inpatient hospitalization or prolongation of existing hospitalization,

The seriousness criteria for hospitalization SHOULD NOT be considered for the following:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- social reasons and respite care in the absence of any deterioration in the subject’s general condition

- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

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

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

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

Any SAEs experienced from the 30 day period after the last study visit only reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to study treatment, complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements on investigator's signature can be found in the investigator folder provided to each site.

If the SAE is previously not documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority

reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

Pregnancies

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

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up be recorded on the same form and should include an assessment of the possible relationship to the study treatment to any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors will be recorded in the CRF as AEs with contributing factors captured as concomitant medication or procedures as appropriate

Please refer to Table 16-4 in Appendix 16.11 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Appendix 16.11, Table 16-4 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-5. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.2.2 Renal safety monitoring

To date, there has been no safety signal for nephrotoxicity with secukinumab in over 12,000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney. All subjects with laboratory tests resulting in clinically significant abnormal values (see Appendix 1 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the MedDRA terminology.

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis.

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

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject 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 subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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

12 Data analysis and statistical methods

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

Unless otherwise specified, p-values will be presented as 2-sided p-values and the type I error rate (alpha) will be 5%.

Inferential efficacy comparisons with placebo will generally focus on the first 16 weeks of treatment unless otherwise specified.

Efficacy and safety data for the placebo-controlled period (or the entire treatment period as appropriate) will be presented by treatment groups. Subjects may be included in more than one treatment group for some analyses (e.g. exposure-adjusted AEs over the entire treatment period).

Note that the treatment groups for a subject may differ depending on the time period of the analysis and whether one assesses the subject for efficacy or safety (see Section 12.1 for details).

Data may also be presented by a combination of the 'original' and 'switch' treatment groups. These treatment groups represent the treatment combinations the subjects experience over the course of the entire trial.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The following analysis sets will be used in this trial:

Randomized set: The randomized set will be defined as all subjects who were randomized. Unless otherwise specified, mis-randomized subjects (mis-randomized in Interactive Voice Response (IVR) will be excluded from the randomized set.

Mis-randomized subjects are defined as those subjects who were mistakenly randomized into the IVR prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized subjects are treated as screen failures.

Full analysis set (FAS): The FAS will be comprised of all subjects from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization, but with actual anti-TNF status.

Dactylitis subset: The dactylitis subset will include all FAS subjects who have dactylitis at baseline.

Enthesitis subset: The enthesitis subset will include all FAS subjects who have enthesitis at baseline.

Psoriasis subset: The psoriasis subset will include all FAS subject who have >= 3% of the body surface area (BSA) affected by psoriatic skin involvement at baseline.

Nail subset: The nail subset will include all FAS subject who have psoriasis currently in nails at baseline.

Safety set: The safety set includes all subjects who took at least one dose of study treatment during the treatment period. Subjects will be evaluated according to treatment received.

12.2 Subject demographics and other baseline characteristics

Demographics and baseline characteristics

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

The following demographic variables and BSL disease characteristics will be summarized by treatment groups:

- Gender, age, race, ethnicity, weight, height, and BMI
- Anti-TNF treatment history (naïve or inadequate responder), [redacted] and other disease-related measures (e.g. [redacted] presence of enthesitis, presence of dactylitis, time since first diagnosis of psoriatic arthritis, PASDAS, subjects with psoriasis ≥ 3%), number of prior biologic PsA therapies, dose of MTX or other DMARD at randomization.

Medical history

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term.

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

12.3 Treatments

Study treatment

The analysis of study treatment data will be based on the safety set. The number of active and placebo administrations received will be presented by treatment group.

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

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

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

Significant prior and concomitant non-drug therapies and procedures will be summarized by primary system organ class and MedDRA preferred term.

The number and percentage of subjects receiving prior and concomitant PsA therapy will be presented by randomized treatment group as well as the reasons for stopping their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other).

12.4 Analysis of the primary endpoint(s)

Details of the testing strategy including primary and secondary endpoints are provided in Section 12.5.

12.4.1 Definition of primary endpoint(s)

The primary efficacy variable will be ACR50 response at Week 16. The analysis of the primary efficacy variable will be based on the FAS subjects. Primarily, CRP will be used instead of ESR to calculate ACR response; ESR will only be used in the event CRP is missing.

The primary estimand is defined as follows:

A. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted psoriatic arthritis population

B. Variable: composite of remaining on the study and on randomized treatment through 16 weeks and achieving ACR50 response at 16 weeks

C. Intercurrent event: the intercurrent event is captured through the variable definition

D. Population-level summary: Difference in marginal response proportions for comparison between treatments

12.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypothesis for ACR50 being tested is that there is no difference in the proportion of subjects fulfilling the ACR50 criteria at Week 16 in i.v. secukinumab vs. placebo regimen.

Let p_j denote the proportion of ACR50 responders at Week 16 for treatment regimens j, j=0, 1 where

- 0 corresponds to placebo regimen,
- 1 corresponds to i.v. regimen,

In statistical terms, H_1: $p_1 = p_0$, H_{A1}: $p_1 \neq p_0$, for the i.v. secukinumab regimen, i.e.

H_1: The i.v. secukinumab. regimen is not different to placebo regimen with respect to signs and symptoms (ACR50 response) at Week 16

The primary endpoint of ACR50 at Week 16 in the FAS will be evaluated using a logistic regression with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate. Difference in marginal response proportions will be computed for comparisons of i.v. secukinumab vs. placebo regimen utilizing the logistic regression model fitted.

12.4.3 Handling of missing values/censoring/discontinuations

Missing data for ACR50 response and other binary efficacy variables (e.g. ACR20, [redacted] HAQ-DI© response, etc.) for data up to Week 16 will be handled as follows:

- Subjects who drop out of the trial for any reason will be considered non-responders from the time they drop out through Week 16 based on the estimands.
- Subjects 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 core set variables) at BSL and at the specific time point will be classified as non-responders.

Continuous variables (e.g. [redacted], etc.) will be analyzed using a mixed-effects repeated measures model (MMRM) which is valid under the missing at random (MAR) assumption. For analyses of these parameters, if all post-BSL values are missing then these missing values will not be imputed and this subject will be removed from the analysis of the corresponding variable, i.e. it might be that the number of subjects providing data to an analysis is smaller than the number of subjects in the FAS.

12.4.4 Sensitivity and Supportive analyses

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

Sensitivity analyses

In order to determine the robustness of the logistic regression model used for the primary analysis, ACR50 response at Week 16, further logistic regression models may be conducted which explore the impact of other BSL or disease characteristics on response.

Supportive analyses

The impact of missing data on the analysis results will be assessed as well by repeating the logistic regression model using ways to handle missing data. These may include, but are not limited to:

- Tipping point analysis

Additional supportive analyses will be conducted to examine the effect of TNFα status (naïve or IR) and/or other cDMARDs along with study drug and/or the effect of treatment discontinuation without rescue medication but remaining in the study on the primary endpoint.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy [redacted] endpoint(s)

Efficacy variables

The secondary efficacy variables are listed below. Secondary efficacy variables will be analyzed using the FAS population unless otherwise specified.

- ACR20 response at Week 16
- Minimal disease activity (MDA) response at Week 16

- PASI90 response for psoriasis subset at Week 16
- Change from baseline in PASDAS score at Week 16
- Change from baseline in HAQ-DI© score at Week 16
- Change from baseline in SF36-PCS at Week 16
- Change from baseline in FACIT-Fatigue score at Week 16
- Change from baseline in mNAPSI for nail subset at Week 16
- Resolution of dactylitis for dactylitis subset at Week 16
- Resolution of enthesitis for enthesitis subset at Week 16

Testing strategy

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

Primary objectives

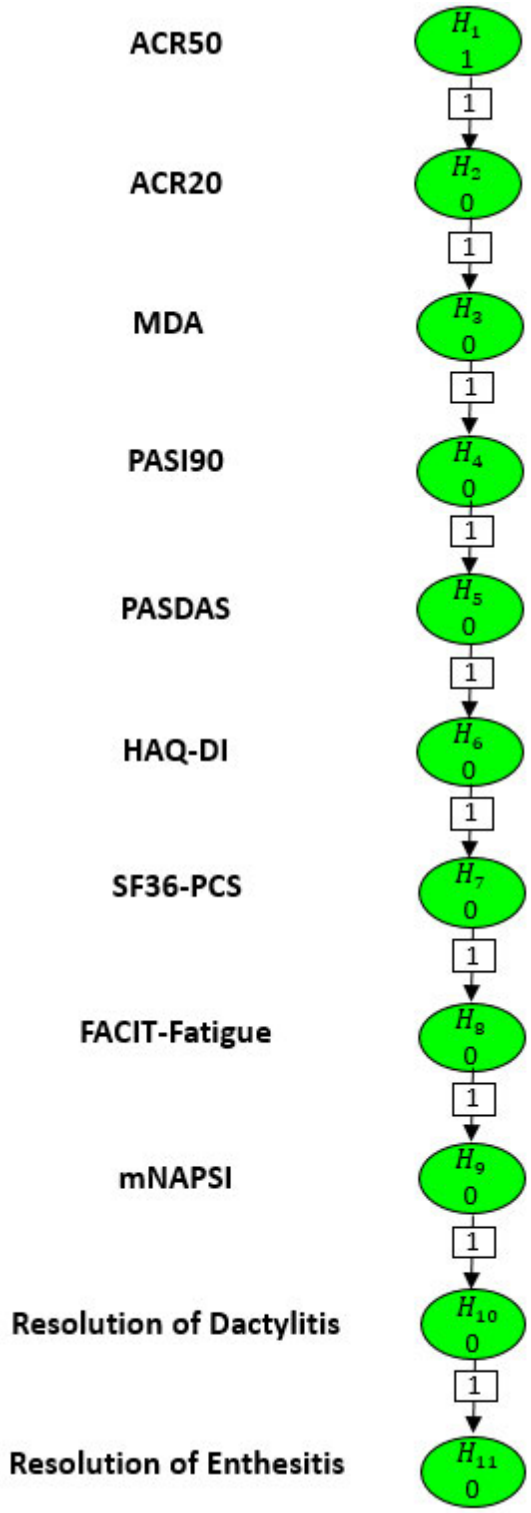
- H_1: i.v. secukinumab regimen is not different to placebo regimen with respect to ACR50 response at Week 16

Secondary objectives

- H_2: i.v. secukinumab regimen is not different to placebo regimen with respect to ACR20 response at Week 16
- H_3: i.v. secukinumab regimen is not different to placebo regimen with respect to MDA response at Week 16
- H_4: i.v. secukinumab regimen is not different to placebo regimen with respect to PASI90 response at Week 16 in the subset of subjects who have ≥3% skin involvement with psoriasis at baseline
- H_5: i.v. secukinumab regimen is not different to placebo regimen with respect to the change from baseline in PASDAS at Week 16
- H_6: i.v. secukinumab regimen is not different to placebo regimen with respect to the change from baseline in HAQ-DI© score at Week 16
- H_7: i.v. secukinumab regimen is not different to placebo regimen with respect to change from baseline in SF36-PCS score at Week 16
- H_8: i.v. secukinumab regimen is not different to placebo regimen with respect to change from baseline in FACIT-Fatigue score at Week 16
- H_9: i.v. secukinumab regimen is not different to placebo regimen with respect to change from baseline in mNAPSI score at Week 16 in the subset of subjects with PsA and nail psoriasis at BSL.
- H_{10}: i.v. secukinumab regimen is not different to placebo regimen with respect to resolution of dactylitis response at Week 16 in the subset of subjects who have dactylitis at BSL.
- H_{11}: i.v. secukinumab regimen is not different to placebo regimen with respect to resolution of enthesitis response at Week 16 in the subset of subjects who have enthesitis at BSL.

The graphical approach of (Bretz et al 2009) for sequentially rejective testing procedures is used to illustrate the testing strategy:

Figure 12-1 Hierarchical Testing Strategy



The family-wise error will be set to two-sided α=5% and it will be controlled with the proposed hierarchical testing strategy.

The hypotheses (H_1) for the primary objective (ACR50 at Week 16) for the i.v. regimen vs. placebo will be tested at α. If H_1 is rejected, then the hypothesis H_2 will be tested at α. If H_2 is rejected, then the hypothesis H_3 will be tested and so on.

Estimand definition for the secondary variables

Estimand definition for the secondary binomial variables is the following:

A. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted Psoriatic arthritis population, unless otherwise specified.

B. Variable: composite of remaining on the study and on randomized treatment through 16 weeks and achieving *variable* response at 16 weeks

C. Intercurrent event: the intercurrent event is captured through the variable definition

D. Population-level summary: Difference in marginal response proportions between treatments

The estimand of binary variables is (i.v. secukinumab regimen vs placebo) obtained from a logistic regression model with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate at week 16 in the FAS population. Difference in marginal response proportions will be computed for comparisons of i.v. regimen vs. placebo regimen utilizing the logistic regression model fitted. In the analysis subjects dropping out or being unblinded before week 16 or having missing response data at week 16 are considered as non-responders.

Estimand definition for the secondary continuous variables is the following:

A. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted Psoriatic arthritis population

B. Variable: change from baseline in the *variable* of interest

C. Intercurrent event: had no intercurrent events occured before week 16

D. Population-level summary: difference in variable means between the treatment conditions

The estimand of continuous variables at week 16 is (i.v. regimen vs placebo) obtained from a repeated measures model in the FAS population assuming subjects dropping out or having missing data at week 16 are missing-at-random (MAR). MAR imputation will be implemented through an MMRM model.

ACR20 at Week 16

Response at Week 16 to ACR20 in the FAS will be evaluated using a logistic regression model with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate. Difference in marginal response proportions will be computed for comparisons of i.v. regimen vs. placebo regimen utilizing the logistic regression model fitted.

Minimal disease activity

The proportion of subjects achieving minimal disease activity (MDA) (Coates et al 2010) which is assessed as 5 of the 7 following: ≤ 1 tender joint count, ≤ 1 swollen joint count, PASI ≤ 1 or

BSA≤3%, patient pain VAS ≤ 15, patient global assessment of disease activity VAS ≤ 20, HAQ-DI© ≤ 0.5, tender entheseal points ≤ 1).

Logistic regression model with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate will be used. Difference in marginal response proportions will be computed for comparisons of i.v. regimen vs. placebo regimen utilizing the logistic regression model fitted.

PASI90 response

PASI90 at Week 16 will be evaluated for those subjects in whom the assessment occurred due to sufficient skin involvement (at least 3% BSA affected with psoriasis, which is planned to be a subset of the FAS). These binary variables will be evaluated in the same fashion as ACR response, i.e. a logistic regression model with treatment and randomization strata as factors and weight as a covariate.

Psoriatic Arthritis Disease Activity Score (PASDAS)

Between-treatment differences in the change in PASDAS will be evaluated using a Mixed effect Repeated Measures model (MMRM) with treatment regimen, analysis visit and TNF-alpha inhibitor status as factors, and weight and BSL PASDAS score as continuous covariates. Treatment by analysis visit and BSL by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for this model. The significance of the treatment effects for i.v. regimens at different analysis visits will be determined from the pairwise comparisons performed between i.v. regimens and placebo at the appropriate analysis visits.

Physical function (HAQ-DI©)

Between-treatment differences in the change in HAQ-DI© will be evaluated using a MMRM with treatment regimen, analysis visit and TNF-alpha inhibitor status as factors, and weight and BSL HAQ-DI© score as continuous covariates. Treatment by analysis visit and BSL by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for this model. The significance of the treatment effects for i.v. regimens at different analysis visits will be determined from the pairwise comparisons performed between i.v. regimens and placebo at the appropriate analysis visits.

SF36-PCS

Between-treatment differences in the change from baseline for SF36-PCS summary score will be evaluated using a MMRM with treatment group, analysis visit and TNF-alpha inhibitor status as factors and BSL SF-36 score and weight as continuous covariates. Treatment by analysis visit and BSL SF-36 score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the treatment effects for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

FACIT-Fatigue©

Between-treatment differences in the change from baseline for FACIT-Fatigue© scores will be evaluated using a MMRM with treatment group, analysis visit and TNF-alpha inhibitor status

as factors and BSL and weight as continuous covariates. Treatment by analysis visit and BSL by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the treatment effects for i.v. regimens at different analysis visits will be determined from the pairwise comparisons performed between i.v. regimens and placebo at the appropriate analysis visits.

Modified Nail Psoriasis Severity Index (mNAPSI)

Between-treatment differences in the mNAPSI change from baseline for scores will be evaluated using a MMRM with treatment group, analysis visit and TNF-alpha inhibitor status as factors and BSL and weight as continuous covariates. Treatment by analysis visit and BSL by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the treatment effects for i.v. regimens at different analysis visits will be determined from the pairwise comparisons performed between i.v. regimens and placebo at the appropriate analysis visits (Cassel et al 2007).

Dactylitis at Week 16

Presence of dactylitis at Week 16 in the subset of subjects who have dactylitis at BSL will be evaluated using a logistic regression model with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate.

Enthesitis at Week 16

Presence of enthesitis at Week 16 in the subset of subjects who have enthesitis at BSL will be evaluated using a logistic regression model with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate.

12.5.2 Safety endpoints

Adverse events

Treatment emergent AEs (events that started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized up to 12 weeks (84 days) after the last dose.

AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a subject reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a subject reported more than one AE within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable. SAEs will also be summarized.

These summaries may be presented separately by placebo controlled period and entire study..

As appropriate, the incidence of AEs will be presented per 100 subject years of exposure.

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

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

Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, serum chemistry and urinalysis). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both BSL and post- BSL.

In addition, shift tables were also presented comparing baseline laboratory result expressed as Common Terminology Criteria for Adverse Events (CTCAE) grade with the worst results up to Week 16 and entire treatment period.

[redacted]

Vital signs

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

[redacted]

[redacted]

12.5.7 Patient reported outcomes

HAQ-DI, SF36, and FACIT-Fatigue are described in Section 12.5.1 for secondary endpoints, [redacted]

[redacted]

[redacted]

12.7 Interim analyses

The primary endpoint analysis will be performed in an interim analysis after all subjects have completed the Week 16 visit. The investigators, site personnel and monitors will continue to remain blinded to the original treatment assignment that each subject received at randomization until after the database lock for Week 60 analysis.

Subsequent to the primary endpoint analysis, additional analyses are planned after subjects have completed the Week 60 assessments and may be used for regulatory submission and/or publication purposes. The final analysis will be conducted after all subjects complete the study. Additional analyses may be performed to support interactions with health authorities, as necessary.

12.8 Sample size calculation

An overall type I error (2-sided) 5% will be used to control type I error. Since one i.v. regimen will be tested versus placebo with respect to the primary endpoint (ACR50 response at Week 16), the type-I-error is 5% two-sided for comparison. The total sample size of 190 subjects per each group is deemed appropriate to achieve adequate power for the primary and secondary endpoints for this study.

12.8.1 Primary endpoint(s)

Analysis of a phase III study (FUTURE 5) showed a placebo response rate of 8.1%, secukinumab 150 mg with SC loading response rate of 35.9%, and secukinumab 300 mg with SC loading response rate of 39.6% at week 16 for ACR50. Assuming that the response rate of i.v. regimen is between the response rates of secukinumab 150 mg with SC loading and 300 mg with SC loading, 190 subjects per group would yield approximately 99% power to detect a treatment difference between 27.8% (based on the difference between secukinumab 150 mg with SC loading and Placebo) and 31.5% (based on the difference between secukinumab 300 mg with SC loading and Placebo) for the primary endpoint of ACR50 in the FAS population (two-sample Chi-Squared Test, Nquery 7.0).

Table 12-1 Summary of power for binary primary endpoint

Endpoint (Week 16)	Placebo Response Rate	Secukinumab with 150 mg SC loading		Secukinumab with 300 mg SC loading	
ACR50	8.1%	Response Rate 35.9%	Power N=190/arm 99%	Response Rate 39.6%	Power N=190/arm 99%

12.8.2 Secondary endpoint(s)

A summary of the assumptions and power for the primary and secondary efficacy parameters using the FUTURE5 study week 16 data is shown in the Table 12-2 for binary endpoints and Table 12-3 for continuous endpoints.

Table 12-2 Summary of power for binary secondary endpoints

Endpoint (Week 16)	Placebo Response Rate	Secukinumab with 150 mg SC Loading		Secukinumab with 300 mg SC Loading	
		Response Rate	Power N=190/arm	Response Rate	Power N=190/arm
ACR50	8.1%	35.9%	99%	39.6%	99%
MDA	7.8%	27.7%	99%	32.4%	99%
PASI90	9.3%	36.8%	99%	53.6%	99%
ACR20	27.4%	55.5%	99%	62.6%	99%
Resolution of Enthesitis	35.4%	54.6%	80%	55.7%	84%
Resolution of Dactylitis	32.3%	57.5%	83%	65.9%	98%

Table 12-3 Summary of power for continuous secondary endpoints

Endpoint (Week 16)	Placebo Mean change from baseline	Secukinumab with 150 mg SC Loading			Secukinumab with 300 mg SC Loading		
		Mean change from baseline	Common standard deviation	Power N=190/arm	Mean change from baseline	Common standard deviation	Power N=190/arm
HAQ-DI	-0.21	-0.44	0.507	99%	-0.55	0.508	99%
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mNAPSI	-2.49	-9.31	9.503	99%	-9.18	9.503	99%
FACIT	1.98	6.18	9.303	99%	6.8	9.303	99%
SF36-PCS	1.83	6.3	7.304	99%	7.62	7.33	99%
PASDAS	-0.91	-2.02	1.359	99%	-2.37	1.361	99%

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must 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 subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

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

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials.

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

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

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

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

15 References

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests.

Clinically notable values will be forwarded to Novartis at the same time that they are sent to investigators. Any action based on these laboratory values should be discussed with Novartis personnel.

Table 16-1 Safety Analyses: Expanded Limits and Notable Criteria

		Notable Criteria	
Laboratory Variable		Standard Units	SI Units
LIVER FUNCTION AND RELATED VARIABLES			
SGOT (AST)		>3 x ULN	>3 x ULN
SGPT (ALT)		>3 x ULN	>3 x ULN
Bilirubin		>2 x ULN	>2 x ULN
Alkaline phosphatase		>2.5 x ULN	>2.5 x ULN
RENAL FUNCTION, METABOLIC AND ELECTROLYTE VARIABLES			
Creatinine (serum)		>2 x ULN	>2 x ULN

HEMATOLOGY VARIABLES

Hemoglobin: 20 g/L decrease from baseline

Platelet count: <100x10E9/L

White blood cell count: <0.8 x LLN

Neutrophils: <0.9 x LLN

16.2 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 et al 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.

1. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination (**1 point**)
2. A negative test result for the presence of rheumatoid factor by any method except latex (**1 point**)
3. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist (**1 point**)
4. Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot (**1 point**)

Total score: _____

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

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

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

Number of tender joints:

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

During the open label phase of the study, as far as 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:

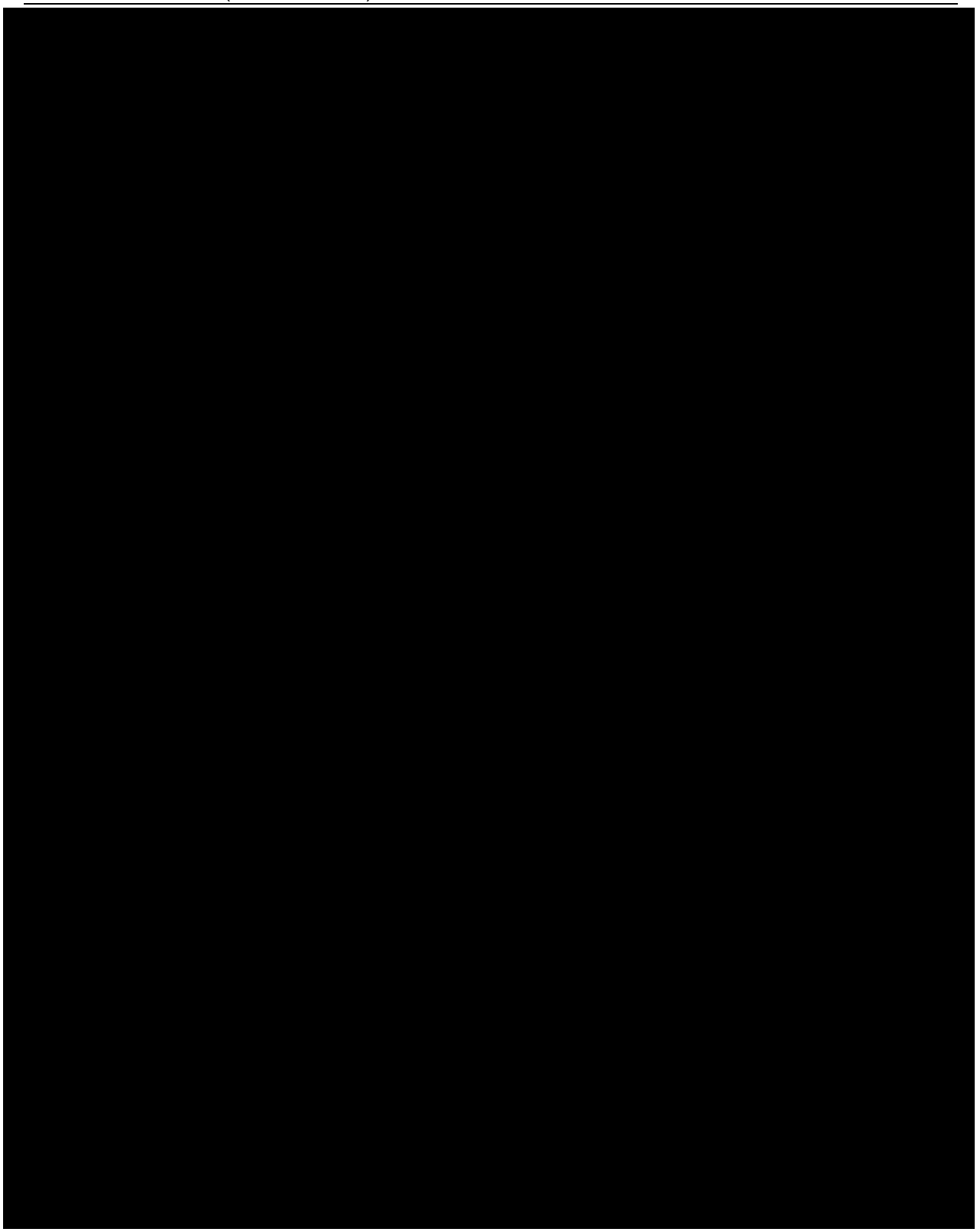
a. Patient's assessment of pain,
b. Patient's global assessment of disease activity,
c. Physician's global assessment of disease activity,
d. Health Assessment Questionnaire (HAQ©) score,
e. C-reactive protein (CRP)/Erythrocyte Sedimentation Rate (ESR).

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

[redacted]

Reference: (Felson et al 1995)

[redacted]



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

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The

severity of disease is calculated as follows. In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20% and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and desquamation (scaling), which are each rated on a scale of 0 to 4. The scoring system for the signs of the disease (erythema, induration, and desquamation (scaling)) are:

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

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

0 = no involvement

1 = 1% to 9% involvement

2 = 10% to 29% involvement

3 = 30% to 49% involvement

4 = 50% to 69% involvement

5 = 70% to 89% involvement

6 = 90% to 100% involvement

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

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

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

PASI Scoring Worksheet

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

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

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

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

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

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

f. Add these scores to get the PASI score.

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

‡ Area scoring criteria (score: % involvement).

0: 0% (clear)

1: <10%

2: 10-<30%

3: 30-<50%

4: 50-<70%

5: 70-<90%

6: 90-100%

Derived from Feldman SR, Krueger GG (2005). Psoriasis assessment tool in clinical trials. Ann Rheum Dis; 64 (Suppl 2);ii65-8, ii69-73.

16.7 Appendix 7:The modified Nail Psoriasis Severity Index (mNAPSI)

Modified NAPSI Instructions

This tool will ask you to assess each abnormality for each of a subject's fingernails. If you question which grade to give, your answer should be the lower of the grades. Three features or groups of features (pitting, onycholysis and oil-drop dyschromia, and crumbling) of each fingernail will be graded on a scale from 0 to 3, according to the directions below. Four features (leukonychia, splinter hemorrhages, hyperkeratosis, and red spots in the lunula) will be graded as either present or absent for each fingernail. After you have viewed all the fingernails of a subject, consider all aspects of all of the subject's fingernails and place a mark on the visual analog scale giving a global assessment of their fingernails.

1. Onycholysis: Separation of the nail plate from the nail bed. The separated part of the nail is opaque and can have white, yellow, or greenish tinge. If there is a piece of nail missing, estimate where the nail normally would have ended at the end of the nail bed, and count that missing part as involved in onycholysis.

Oil-drop (salmon patch) dyschromia: Reddish-brown discoloration under the nail plate.

Onycholysis and oil-drop dyschromia are considered together. When looking at the nail, combine the total percentage area of the nail that is affected by either and use that combined total to score the nail.

Score	Percent of nail with onycholysis or oil-drop dyschromia present
0	No onycholysis or oil drop dyschromia present
1	1–10% of the nail has onycholysis or oil-drop dyschromia
2	11–30% of the nail has onycholysis or oil-drop dyschromia

3	> 30% of the nail has onycholysis or oil-drop dyschromia

2. Pitting: Small, sharply defined depressions in the nail surface. Pits are discrete abnormalities ("ice-pick-like"). If there is nail plate crumbling that is confluent with pits, do not score for pits. If the pits are separate from crumbling, they may be scored regardless of whether crumbling is present or not.

Score	Number of pits
0	0
1	1–10
2	11–49
3	> 50

3. Nail plate crumbling: Crumbling or fragmentation of friable nail plate which may be associated with confluent pitting. Crumbling involves alteration of the nail plate surface. Horizontal ridging of the nail, "wave-like" appearance, and horizontal lines are all features of crumbling.

Score	Percent of nail with crumbling present
0	No crumbling
1	1–25% of the nail has crumbling
2	26–50% of the nail has crumbling
3	> 50% of the nail has crumbling

The next 4 abnormalities are scored only by their presence or absence. A score of 1 indicates present and a score of zero indicates not present.

1. **Leukonychia**: White spots in the nail plate due to psoriasis in the mid matrix. Leukonychia are just color changes. If it appears that there is depression or irregularity to the nail surface, this may be pitting or crumbling, not leukonychia. If the leukonychia is adjacent to, or confluent with crumbling or pits, it is counted as part of the crumbling or pitting and not as a separate abnormality.
2. **Splinter hemorrhages**: Small, longitudinal, linear, dark brown hemorrhage under the fingernail.
3. **Nail bed hyperkeratosis**: Thickened keratin in the nail bed.
4. **Red spots in the lunula**: Small pink or red macules in the lunula.

16.8 Appendix 8: Standard reference table for the LDI

Table 16-2 Table- hands (in cm)

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

Table 16-3 Table- feet (in cm)

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

16.9 Appendix 9: Health Assessment Questionnaire-Disability Index (HAQ-DI)©

The HAQ-DI© (Fries 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. Subjects 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-DI©

The HAQ-DI© 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 subject requires the use of aids, devices, or help from another to accomplish any of the activities in an associated category, then the score for that category will be assigned the value 2, unless the score is already 3 (i.e. scores of 0 or 1 are increased to 2). Associated categories are defined in the “HAQ PACK”. From the scores for each category a Standard Disability Index (SDI) is computed by summing the computed scores for each category and dividing by the number of categories answered. The SDI is not computed if the subject does not have scores for at least 6 categories. This SDI is the HAQ-DI© score, which will be used in the statistical analyses of this instrument. The range for this score is (0, 3).

HAQ-DI© Data Collection

The HAQ-DI© is to be completed by the subject in their local languages, using an electronic device. The questionnaires should be completed by the subjects in a quiet area free from disturbance, and before any visit assessments. Subjects 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 subject's responses without influencing their answers. The information provided is strictly confidential and will be treated as such. If a subject has missed a question or given more than one response per question, then this should be brought to subject. Incomplete questions should not be accepted without first encouraging the subject to complete unanswered questions.

16.11 Appendix 11: Liver event and laboratory trigger definitions and follow-up requirements

Table 16-4 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	3 x ULN < ALT / AST ≤ 5 x ULN 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN ALP > 2 × ULN (in the absence of known bone pathology) TBL > 2 × ULN (in the absence of known Gilbert syndrome)

	ALT or AST > 3 × ULN and INR > 1.5
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any adverse event potentially indicative of a liver toxicity *

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

TBL: total bilirubin; ULN: upper limit of normal

Table 16-5 Follow up Requirements for Liver Events and Laboratory Triggers

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

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

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

TBL: total bilirubin; ULN: upper limit of normal

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

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

Criteria	Actions required	Follow-up monitoring

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

16.12 Appendix 12: Guidelines for administering the PRO questionnaires

Before trial start

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

For example, one question in the SF-36 asks 'How much of the time in the past 4 weeks- have you felt downhearted and blue?' If a subject responds 'most or all of the time', then the study coordinator should inform the study investigator.

Before completion

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

Subjects should have adequate space and time to complete the forms

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

Questionnaire should be administered before the clinical examination

During completion

Administrator may clarify the questions but should not influence the response

Only one response for each question

Also see "Addressing Problems and Concerns"

After completion

Check for completeness and not for content*

Data should be sent from the eCRF / electronic device

Data should be reviewed by Investigator for AEs

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

Addressing Problems and Concerns

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

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

Tell the subject that completion of the questionnaire(s) is voluntary. The goal is to better understand the physical, mental and social health problems of subjects. Emphasize that such information is as important as any other medical information and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the respondent has filled in the past. If the subject still declines, retrieve the questionnaires. Record the reason for the decline and thank the subject.

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

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

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

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

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

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

The subject 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 subject that his/her answers will be pooled with other subjects' answers and that they will be analyzed as a group rather than as individuals. Tell the subject that completed forms are not routinely shared with treating staff and that their responses will only be seen by you (to check for completeness) and by the investigator. Any response which may directly impact on or reflect their medical condition (*e.g.* noting of severe depression) will be communicated by the coordinator to the physician.

The subject asks the meaning of a question/item

While completing the questionnaire, some subjects might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the subject by rereading the question for them *verbatim.* If the subject 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. Subjects should answer the questions based on what *they* think the questions mean.

A General Information about all questionnaire(s):

All questionnaires have to be completed by the subjects in their local languages using an electronic device. The questionnaires should be completed by the subjects in a quiet area free from disturbance, and before any visit assessments. Subjects 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 subject's responses without influencing their answers. The information provided is strictly confidential and will be treated as such. If a subject has missed a question or given more than one response per question, then this should be brought to subject. Incomplete questions should not be accepted without first encouraging the subject to complete unanswered questions.

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