

# Protocol

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## **Secukinumab Interleukin-17A Inhibition in Psoriatic Arthritis – 14-12679.R1**

Submission to NEJM

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

Clinical Development

Secukinumab (AIN457)

CAIN457F2306

**A randomized, double-blind, placebo-controlled,  
multicenter study of secukinumab to demonstrate the  
efficacy at 24 weeks and to assess the long term safety,  
tolerability and efficacy up to 2 years in patients with active  
psoriatic arthritis**

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## List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANA	Anti-nuclear antibodies
Anti-CCP	Anti-cyclic citrullinated peptide
AS	Ankylosing Spondylitis
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BMI	Body Mass Index
BSL	Baseline
CASPAR	CLASification criteria for Psoriatic Arthritis
CFR	Code of Federal Regulations (US)
CRF	Case Report/Record Form
CRD	Clinical Research and Development
CPO	Country Pharma Organization
CRO	Contract Research Organization
CRP/hsCRP	C-reactive protein / high sensitivity C-reactive protein
CSR	Clinical Study Report
CTEP	Cancer Therapy Evaluation Program
DAS	Disease Activity Score
DMARD	Disease Modifying Antirheumatic Drug
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic acid
DS&E	Drug Safety and Epidemiology
dsDNA	Anti-double stranded DNA antibodies
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EMA/EMEA	European Medicines (Evaluation) Agency
EULAR	European League Against Rheumatism
ESR	Erythrocyte Sedimentation Rate



FACIT-Fatigue <sup>®</sup>	Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GEE	Generalized estimating equation
HAQ-DI <sup>®</sup>	Health Assessment Questionnaire – Disability Index
HIV	Human Immunodeficiency Virus
HRQoL	Health-related Quality of Life
hsCRP	High sensitivity C-Reactive Protein
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGA mod 2011	Novartis Investigator’s Global Assessment modified 2011
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	IntraUterine Device
IUS	IntraUterine System
i.v.	intravenous(ly)
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDI	Leeds Dactylitis Index
LDL	Low Density Lipoprotein
LEI	Leeds Ethesitis Index
LLN	Lower limit of normal
LOCF	Last observation carried forward
LLOQ	Lower Limit of quantification
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeter mercury
MMP	Matrix Metalloprotease

MRI	Magnetic Resonance Imagin
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PG	Pharmacogenetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PoC	Proof of Concept
PPD	Purified protein derivative
PRN	As required
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
PsAMRIS	Psoriatic Arthritis Magnetic Resonance Imaging Scoring System
QoL	Quality of Life
RA	Rheumatoid Arthritis
RBC	Red Blood Cells
RF	Rheumatoid Factor
SAE	Serious adverse event
s.c.	subcutaneous(ly)
SCR	Screening
SJC	Swollen Joint Count
SNP	Single Nucleotide Polymorphism
SpA	Spondyloarthritidies
SWFI	Sterile water for injection
t.i.d.	ter in die, three times daily
TJC	Tender Joint Count
TNF	Tumor necrosis factor
ULN	Upper limit of normal
US	Unites States of America
VAS	Visual Analog Scale
WBC	White Blood Cells
WHO	World Health Organization

WPAI-GH

Work Productivity and Activity Impairment–General Health  
questionnaire

## Glossary of terms

Assessment	A procedure used to generate data required by the study
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
Enrollment	Point/time of patient 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)
Inadequate response to TNF $\alpha$	Active disease despite stable treatment with anti-TNF $\alpha$ for at least 3 months at a stable dose or for at least one dose in the case of lack of tolerance
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 is synonymous with "investigational new drug."
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Phase	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Premature patient withdrawal	Point/time when the patient 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 patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

## Protocol synopsis

**Title of study:** A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the safety, tolerability and long term efficacy up to 2 years in patients with active psoriatic arthritis

**Purpose and rationale:** The purpose of this 2 year study is to demonstrate efficacy on signs and symptoms of psoriatic arthritis and to assess the long term safety, tolerability and efficacy on joint/bone structure of secukinumab given as intravenous (i.v.) loading doses, followed by sub-cutaneous (s.c.) injections of two dose levels of secukinumab versus placebo in patients with active PsA. Efficacy at Week 24 will be assessed based on signs and symptoms according to the American College of Rheumatology response criteria (ACR 20 response), whereas long term efficacy will be based on joint/bone structural preservation (X-ray) and physical function (HAQ-DI), as well as skin assessment for psoriasis signs. Treatment will continue up to 2 years to assess inhibition of joint damage and physical function.

### Objectives:

Primary objective: To demonstrate that the proportion of patients achieving ACR20 response criteria at Week 24 is greater on secukinumab as compared to placebo in the subgroup of patients who are TNF $\alpha$  inhibitor naïve.

Key secondary objectives:

1. The proportion of subjects achieving ACR20 response criteria at Week 24 is greater on secukinumab as compared to placebo in the entire study population.
2. The improvement (change) from baseline on secukinumab is superior to placebo for the HAQ-DI after 24 weeks of treatment in the subgroup of subjects who are TNF $\alpha$  inhibitor naïve.
3. The improvement (change) from baseline to Week 24 on secukinumab is superior to placebo for joint/bone structural damage (van der Heijde modified total Sharp score) in the subgroup of subjects who are TNF $\alpha$  inhibitor naïve.
4. 12 months treatment with secukinumab is superior to delayed treatment with secukinumab placebo / secukinumab with regards to the proportion of subjects achieving Major clinical response in the subgroup of subjects who are TNF $\alpha$  inhibitor naïve.

**Population:** The study population will consist of a representative group of rheumatoid factor negative subjects at least 18 years of age, fulfilling the CASPAR criteria for active psoriatic arthritis. Subjects included must report active disease despite current or previous NSAID, DMARD and/or TNF $\alpha$  inhibitor therapy.

Concomitant therapy with MTX ( $\leq$ 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 must have signs of skin manifestations of psoriasis, defined by at least one psoriatic plaque of  $\geq$ 2 cm diameter (but not in armpits, or chest between breasts, or groin) or nail changes consistent with psoriasis or documented history of plaque psoriasis.

Patients cannot be re-screened more than once.

This is a multinational study and it is expected that subjects will be enrolled at approximately 150 sites. About 750 subjects will be screened for approximately 600 subjects to be randomized). A screening failure rate of 30 % and post-randomization drop out rate of 25 % is anticipated. Enrollment will stop as soon as the target number of randomized subjects is reached.

### Inclusion/Exclusion criteria:

Inclusion criteria:

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

1. Male or non-pregnant, non-lactating female subjects at least 18 years of age
2. 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**  $\geq 3$  tender joints out of 78 and  $\geq 3$  swollen out of 76 (dactylitis of a digit counts as one joint each)
3. Rheumatoid factor and anti-CCP antibodies negative
4. Diagnosis of active plaque psoriasis, with at least one psoriatic plaque of  $\geq 2$  cm diameter (but not in intertriginous areas such as armpits, or chest between breasts, or groin) or nail changes consistent with psoriasis or documented history of plaque psoriasis

Exclusion criteria:

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Chest X-ray with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician
2. Subjects who have previously been treated with more than 3 different TNF $\alpha$  inhibitors (investigational or approved)
3. Subjects taking high potency opioid analgesics (e.g., methadone, hydromorphone, or morphine)
4. Subjects who have ever received biologic immunomodulating agents except for those targeting TNF $\alpha$ , investigational or approved
5. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor
6. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)

**Investigational and reference therapy:** At baseline, eligible patients will be randomized to one of the following three treatment arms in a ratio of 1:1:1.

- Group 1: secukinumab i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then secukinumab 75 mg s.c. starting at Week 8 and injected every 4 weeks
- Group 2: secukinumab i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks
- Group 3: Placebo i.v. at BSL, Weeks 2 and 4 then placebo s.c. starting at Weeks 8 and 12.

At Week 16 (Visit 8), subjects will be classified as responders ( $\geq 20\%$  improvement from baseline in both tender and swollen joint counts) or non-responders and will be re-assigned/re-randomized at **Week 16** by the IRT to receive double-blind treatment up to 2 years, as follows:

- Subjects on placebo (Group 3) who are non-responders will be re-randomized to receive secukinumab 75 mg s.c. or 150 mg s.c. (1:1) every 4 weeks
- Subjects on placebo (Group 3) who are responders will continue to receive secukinumab placebo every 4 weeks until Week 24. At Week 24, these subjects will be re-randomized to receive secukinumab 75 mg s.c. or 150 mg s.c. (1:1) every 4 weeks regardless of responder status

**Study design:** This pivotal study uses a double-blind, randomized, parallel-group, placebo-controlled design. A screening (SCR) period running 4 weeks before randomization will be used to assess eligibility followed by a treatment period of 2 years.

At Week 24, efficacy of secukinumab treatment will be assessed based on an ACR20 response.

Subjects who complete the 2 year study may be eligible to enter a planned extension trial.

**Efficacy assessments:**

- ACR 20, 50 70

- PsARC response
- Disease Activity Score (DAS28) and EULAR response criteria
- HAQ-DI
- Progression of structural damage by X-ray – van der Heijde total modified Sharp score and subscores
- Leeds Enthesitis Index (LEI)
- Leeds Dactylitis Index (LDI)
- Psoriasis Area and Severity Index (PASI)
- Investigator's Global Assessment (mod 2011) for overall psoriatic disease
- Target lesion assessment
- Modified Nail Psoriasis Severity Index (mNAPSI)
- MRI on hands (incl. wrist) (at selected centers and in TNF $\alpha$  inhibitor naïve patients with a swollen wrist))
- Quality of Life, fatigue, utilities and work productivity (SF-36 v2 Acute Form, FACIT-Fatigue, DLQI, PsAQoL, EQ-5D, WPAI-GH)

**Other assessments:**

- Safety and tolerability: Evaluation of all AEs and SAEs including injection site reactions, vital signs and laboratory assessments
- Smoking history
- Pharmacokinetics
- Soluble plasma protein markers related to targeted pathway and cardiovascular risk markers
- Exploratory: pharmacogenetics
- ANA, anti dsDNA antibodies, anti-CCP antibodies

**Data analysis:**

The primary endpoint in the study is ACR20 at Week 24 for subjects who are TNF $\alpha$  inhibitor-naïve. Key secondary objectives will be to compare secukinumab to placebo according to a sequential testing procedure and include ACR20 for the full population, change from baseline in HAQ-DI for the TNF $\alpha$  inhibitor-naïve subjects, change from baseline in van der Heijde total modified Sharp score TNF $\alpha$  inhibitor-naïve subjects, and major clinical response in TNF $\alpha$  inhibitor-naïve. Safety analyses will include summaries of adverse events, laboratory measurements and vital signs.

## 1 Introduction

### 1.1 Background

Psoriatic arthritis (PsA) is an immune-mediated chronic inflammatory disease belonging to the spectrum of conditions commonly referred to as spondyloarthritides (SpA). The scientific community is split over the question whether to view these conditions together or consider them as separate entities (Nash 2005). For example, inflammatory back pain associated with psoriasis fit two classifications (1) AS 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 (Turiewicz 2007). This latter notion was recently corroborated by findings in a large-scale single nucleotide polymorphism (SNP) scan study, where IL23R 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 2008). Together, a common pathway including the IL-23/IL-17 axis may play a role in seronegative SpAs including psoriatic arthritis.

Psoriatic arthritis is a frequent 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. Recent efforts were aimed at defining more stringent classification criteria for standardized recruitment into clinical trials (Taylor 2006). 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 2004). The majority of patients will have psoriasis prior the associated arthritis occurs and will be under treatment for their skin disease. NSAIDs are used for musculoskeletal pain symptoms. Traditional disease modifying anti-rheumatic drugs (DMARDs) include methotrexate (MTX), sulfasalazine, cyclosporine, and leflunomide and are inadequate for a number of patients because these drugs only partially control established disease (Mease 2008).

Several lines of evidence support the notion of prominent T cell involvement in the pathogenesis of PsA. Memory CD4<sup>+</sup> and CD8<sup>+</sup> cells are present in skin lesions as well as the inflamed synovium that express activation markers and have characteristics of oligoclonal expansion. (Curran 2004, Tassiulas 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 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. In addition, current treatment options for patients with intolerance or an inadequate response to anti-TNF- $\alpha$  agents are limited.

IL-17 antagonism represents a novel therapeutic approach aimed at interference with the chronic inflammatory process by selectively targeting the predominant proinflammatory cytokine of the helper T17 cell subset. Additional effects of anti-IL17 on bone homeostasis via RANKL and IL-1, upstream of TNF $\alpha$ , can be inferred from animal studies (Koenders 2005). Assuming a potential role of TH17 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. Such effects may be additive or synergistic to anti-TNF, and thus may provide 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 a phase II study (CAIN457F2201) in Rheumatoid Arthritis (RA). IL-17A has been shown to play a pivotal direct pathogenetic role in both inflammatory and destructive joint tissue manifestations of RA and has direct effects on matrix metalloprotease (MMP) activation and stimulation of osteoclast-mediated bone resorption (Stamp 2004; Witowski 2004; Moseley 2003). Interim analysis of all 42 patients enrolled in the PsA PoC study CAIN457A2206 who completed week 6, together with preliminary data from the later time points up to week 16, 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. 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. Furthermore, In a completed proof of concept study (CAIN457A2102), the effects of secukinumab administered at 3 mg/kg as a single intravenous infusion were compared with that of placebo in thirty-six subjects with active chronic plaque-type psoriasis. The study demonstrated efficacy at the 4- week endpoint and continuous efficacy at 12 weeks based on Psoriasis Area and Severity Index (PASI) and Investigator's Global Assessment mod 2009 (IGA mod 2011) endpoints.

To date, over 2,000 subjects with a variety of diseases and healthy volunteers have been enrolled into completed and ongoing studies with secukinumab, and over 1,400 subjects have been newly exposed to secukinumab at single and multiple doses ranging from 0.3 mg/kg to 10 mg/kg intravenous (i.v.) and 25 mg to 300 mg subcutaneous (s.c.). Of these, over 300 subjects have been continued on secukinumab through enrollment into extension trials. In total, 333 RA and 61 PsA patients have been enrolled into trials with secukinumab. Full safety results including all reported adverse events are currently available for eight studies (across autoimmune indications) that have been completed. These show comparable numbers of adverse events in subjects treated with secukinumab compared to placebo without indication of any specific organ toxicity. Please refer to the Investigator Brochure for a more detailed review of the pre-clinical and clinical information on secukinumab.

## 1.2 Purpose

The purpose of this study is to demonstrate at Week 24 the efficacy and assess the safety of secukinumab given as intravenous (i.v.) loading doses, followed by sub-cutaneous (s.c.) injections of 2 dose levels of secukinumab versus placebo in subjects with active PsA. At Week 24, efficacy will be assessed based on improvement in signs and symptoms according to the American College of Rheumatology response criteria (ACR20 response), whereas long term efficacy up to 2 years will be based on joint/bone structure preservation (X-ray) and improvement in physical function (HAQ-DI), as well as skin and nail improvement for psoriasis signs.

Data from this study are aimed at supporting a global submission of the psoriatic arthritis indication.

## **2 Study objectives**

### **2.1 Primary objectives**

To demonstrate the efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo in patients with active PsA based on the proportion of patients achieving an ACR20 response in the subgroup of subjects who are TNF $\alpha$  inhibitor naïve.

### **2.2 Key Secondary objectives**

The key secondary objectives of the study are to demonstrate:

- The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving an ACR20 response in the entire study population.
- The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the HAQ-DI at Week 24 in the subgroup of subjects who are TNF $\alpha$  inhibitor naïve.
- The improvement (change) from baseline to Week 24 on secukinumab 75 and 150 mg is superior to placebo for joint/bone structural damage (van der Heijde modified total Sharp score) in the subgroup of subjects who are TNF $\alpha$  inhibitor naïve.
- Secukinumab 75 or 150 mg is superior to placebo (as originally randomized) with regards to the proportion of subjects achieving Major Clinical Response at Week 52 in the subgroup of subjects who are TNF $\alpha$  inhibitor naïve.

### **2.3 Secondary Objectives**

To evaluate the efficacy of secukinumab compared to placebo, as applicable, on:

1. Joint/bone structure preservation at Weeks 52 and 104
2. Erosion and Joint space narrowing (van der Heijde modified Sharp sub scores) at Weeks 24, 52 and 104
3. Proportion of subjects with no joint/bone structural progression (change in van der Heijde modified total Sharp score  $\leq 0$ ) at Weeks 24, 52 and 104.
4. Maintenance of effect by comparing progression in Year 1 (up to Week 52) and Year 2 (Week 52 to Week 104) of the different treatment regimens (van der Heijde modified total Sharp score and subscores).
5. Psoriatic arthritis response criteria (PsARC) and ACR 50 and 70 response at Week 24
6. PsARC, ACR 20, ACR 50 and ACR 70 response at Weeks 1, 2, 4, 8, 12, 16, and 20 and up to Week 104
7. Major Clinical Response at week 104
8. HAQ-DI over time at Weeks 1, 2, 4, 8, 12, 16, 20, and over time up to Week 104
9. ACR components, including markers of inflammation (hsCRP and ESR) at Weeks 1, 2, 4, 8, 12, 16, 20, and 24 and over time up to Week 104

10. Change in Disease Activity Score (DAS) 28-CRP score at Week 1, 2, 4, 8, 12, 16, 20, 24 versus placebo, and over time up to Week 104
11. DAS 28-CRP remission (defined as a DAS28 < 2.6) and low disease activity (defined as DAS28 ≤ 3.2) at Weeks 1, 2, 4, 8, 12, 16, 20, and 24 and over time up to Week 104
12. EULAR response criteria Weeks 1, 2, 4, 8, 12, 16, 20, and 24 and over time up to Week 104
13. Leeds Dactylitis Instrument (LDI) and Leeds Enthesitis Index (LEI) at Weeks 2, 4, 8, 12, 16, and 24 and up to Week 104
14. PASI 75 response, investigator's global assessment for psoriasis, (IGA mod 2011), Target Lesion Score (TLS) and modified Nail Psoriasis Severity Index (mNAPSI) at Weeks 1, 2, 4, 8, 12, 16, and 24 and up to Week 104
15. Quality of life and fatigue (SF-36, FACIT-Fatigue), Psoriatic Arthritis Quality of life (PsAQoL), Dermatology life Quality Index (DLQI), EQ-5D and Work Productivity and Impairment-General Health (WPAI-GH) assessment at Weeks 2, 4, 8, 16, and 24 and over time up to Week 104

AND

16. To evaluate the overall safety and tolerability of secukinumab up to Week 104
17. To investigate the development of immunogenicity against secukinumab

## 2.4 Exploratory objectives

1. To explore the PK/PD relationship of secukinumab
2. To perform exploratory pharmacogenetic assessments to examine whether individual genetic variation in genes relating to drug metabolism, PsA, and the drug target pathway confer differential response to secukinumab
3. To conduct exploratory biomarker assessments aiming to identify potential markers associated with treatment response to secukinumab, or that possibly correlate with the severity or progression of psoriatic arthritis, and to assess the impact of secukinumab on cardiovascular surrogate biomarkers.
4. To measure the effect of secukinumab on joint/bone structure preservation using MRI measurements (modified RAMRIS and JSN score) in the subgroup of subjects who are TNF $\alpha$  inhibitor naïve.

## 3 Investigational plan

### 3.1 Study design

This pivotal phase III study uses a double-blind, randomized, parallel-group, placebo controlled design. A screening period running up to 4 weeks before randomization will be used to assess eligibility followed by a treatment period of two years. At baseline (BSL), subject whose eligibility is confirmed will be randomized to one of three treatment groups:

- Group 1: Secukinumab i.v. (10mg/kg) at BSL, Weeks 2 and 4, then secukinumab 75 mg s.c. starting at Week 8 and injected every 4 weeks
- Group 2: Secukinumab i.v. (10mg/kg) at BSL, Weeks 2 and 4, then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks

- Group 3: Placebo i.v. at BSL, Weeks 2 and 4, then placebo s.c. starting at Week 8 and Week 12.

The subjects will be stratified according to being either TNF $\alpha$  inhibitor incomplete responders (IR) or TNF $\alpha$  inhibitor naïve subjects. 30% of subjects are planned to be TNF $\alpha$  inhibitor inadequate responders to ensure a representative subject population for the assessment of efficacy and safety. Thus, it is planned to randomize approximately 180 TNF $\alpha$  inhibitor IR subjects and 420 TNF $\alpha$  inhibitor naïve subjects.

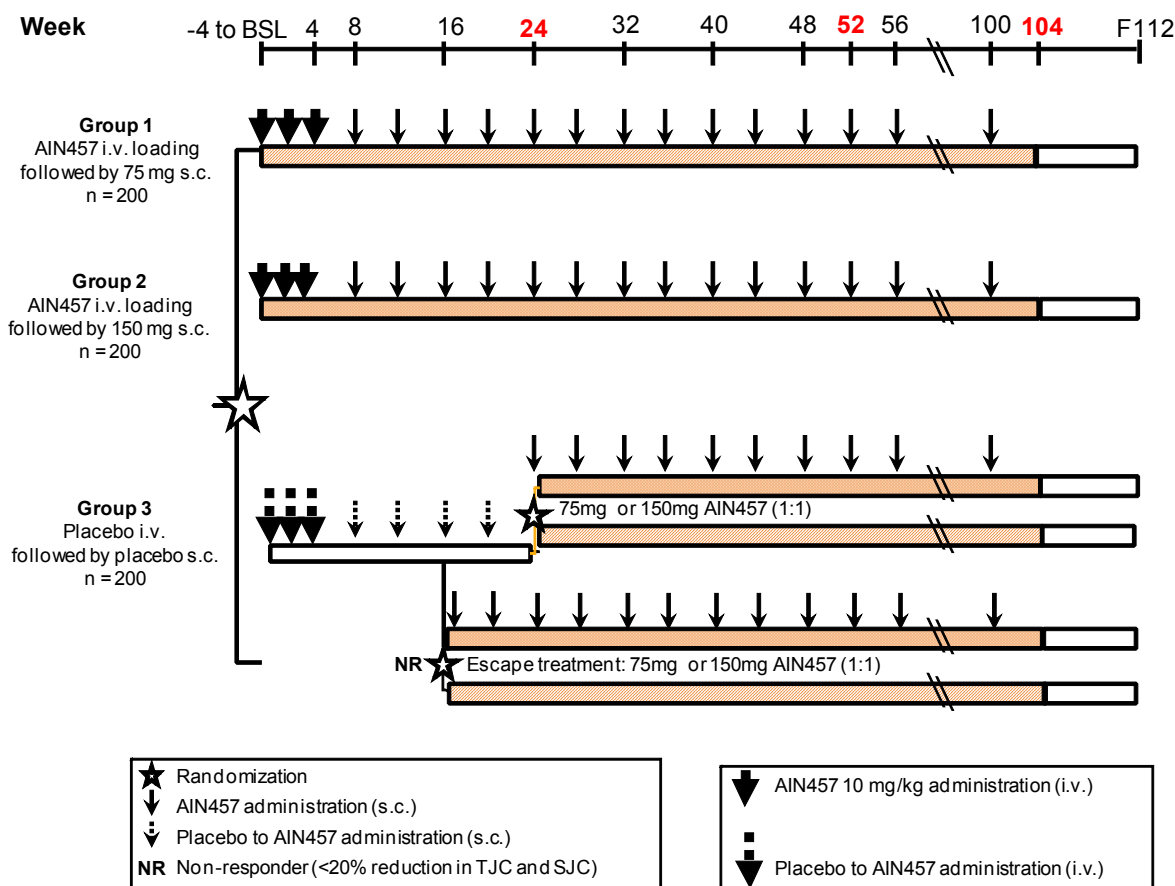
**At Week 16 (Visit 8)**, subjects will be classified as responders ( $\geq 20\%$  improvement from baseline in both tender and swollen joint counts) or non-responders. Subjects who were randomized to placebo at baseline will be re-randomized by the Interactive Response Technology (IRT) to receive double blind treatment up to 2 years, as follows (see [Figure 3-1](#)):

- Subjects on secukinumab placebo (Group 3) who are responders will remain on placebo until week 24. At Week 24, these subjects will be re-randomized (1:1) to receive either secukinumab 75 or 150 mg every 4 weeks
- Subjects on secukinumab placebo (Group 3) who are non-responders will be re-randomized (1:1) at Week 16 to receive either secukinumab 75 mg or 150 mg s.c. every 4 weeks.

Rescue medication will not be allowed until Week 24. However, subjects deemed not to be benefiting from the study treatment by the investigator or for any reason on their own accord will be free to discontinue participation in the study at any time.

Subjects who complete the study may be eligible to enter a planned extension trial.

**Figure 3-1 Study design**



### 3.2 Rationale of study design

The double-blind, randomized, parallel-group placebo controlled design used in this study is aligned with Phase III trials of other biologics and is in accordance with EMA guidelines (EMA 2003). The treatment duration of the placebo group is kept short and the group will be re-assigned to active treatment at the end of the primary endpoint analysis. The blinding is maintained beyond the primary endpoint so as to ensure reliable efficacy and safety measures. The regular assessments of disease activity ensures that subjects who are experiencing worsening of disease in any of the treatment groups can exit the study upon their own wish or based on the advice of the investigator at any time. Long term treatment data up to two years are being generated to demonstrate long-term efficacy and to support the safety database in this population.

### 3.3 Rationale of dose/regimen, duration of treatment

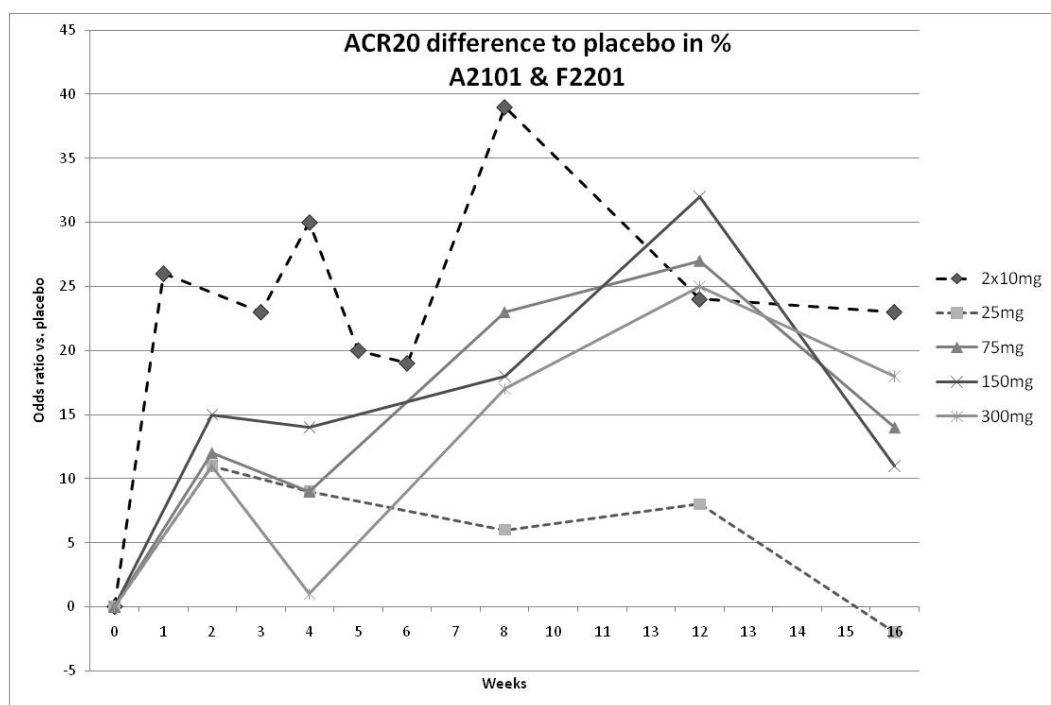
The dosing rationale for psoriatic arthritis (PsA) and ankylosing spondylitis (AS) relies upon the dose-efficacy relationship data obtained in the proof of concept (PoC) studies in Rheumatoid Arthritis (RA) (CAIN457A2101), in Ankylosing Spondylitis (AS) (CAIN457A2209) and in PsA (CAIN457A2206) along with data from the RA dose ranging trial (CAIN457F2201).

Interim analysis of all 42 subjects enrolled in study CAIN457A2206 (dosed with i.v. 2 x 10mg/kg) who completed Week 6, together with preliminary data from the later time points up to Week 16, suggest that a clinically meaningful response 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.

Evidence to support a similar dose-efficacy relationship for secukinumab across the arthritides (RA, AS and PsA) is substantiated by existing evidence which indicates a degree of commonality in the pathways leading to joint damage in these chronic inflammatory diseases and a comparatively similar acute phase response and cytokine profile in the pathogenesis of the diseases. In further support of common inflammatory pathways all three conditions are responsive to both anti-IL17 and anti-TNF $\alpha$  therapy.

In the RA PoC study (CAIN457A2101), two doses of secukinumab 10 mg/kg i.v. administered at BSL and Week 3, achieved an ACR20 of 46% at Week 6 and 54% at Week 16 compared to a placebo response of 27% and 31% respectively at these time points. In contrast fixed doses of secukinumab administered at BSL and then every 4 weeks at 75, 150 and 300 mg in the RA Ph II study (CAIN457F2201) achieved an ACR20 of 48%, 40% and 39% at Week 8 and 50%, 47% and 54% at Week 16. However, placebo responses in this trial were 24% at Week 8 and 36% at Week 16. Thus the i.v. regimen employed in the PoC trial resulted in a 19% improvement in ACR20 over placebo at Week 6 and 23% at Week 16 (Figure 3-2). The fixed monthly doses of secukinumab at 75, 150 mg and 300 mg resulted in 24%, 16% and 15% improvement in ACR20 over placebo at Week 8 and 14%, 11% and 18% respectively at Week 16 (Figure 3-2). These data suggest that early high doses of secukinumab lead to increased efficacy in the first 8 weeks. Based upon these data currently planned Phase III studies in RA will be employing an i.v. loading regimen induction therapy with 10 mg/kg secukinumab administered at BSL, 2 and 4 followed by monthly secukinumab s.c. at either 75 mg or 150 mg.

**Figure 3-2 Placebo corrected ACR20 over time comparing two doses of secukinumab 10 mg/kg i.v. at BSL and 3 (CAIN457A2101) to fixed s.c. doses of secukinumab every 4 weeks (CAIN457F2201)**



To define the optimal dose for maintenance ACR, DAS28 and HAQ efficacy parameters were considered based on study CAIN457F2201. Data available from this study up to 24 weeks indicates that efficacy responses can be maintained or improved with the proposed monthly doses of 75 or 150 mg s.c..

The efficacy data from the RA study CAIN457F2201 showed that at Week 24 in the overall population as originally randomized ACR20 responses were 38 % for 25 mg, 57% for 75 mg, 58% for 150 mg and 51% for 300 mg. Non-responders in the 25 and 75 mg dose had received 1 dose of 150mg at Week 20 and non-responders in the 150 mg group had received one dose of 300 mg at Week 20. Subjects in the 300 mg cohort remained on 300 mg. Subjects switched from placebo to 150 mg after week 16 attained a 56% ACR 20 response by Week 24. These data indicate that 25 mg has similar efficacy to placebo and that 75 mg and 150 mg provided the best efficacy.

Both 75 mg and 150 mg s.c. dosed every 4 weeks in maintenance are proposed based on the totality of the data from CAIN457F2201 for phase III for the following reasons:

- 1) To ensure optimal assessment of efficacy potential for ACR responses using 2 effective s.c. doses used in phase II.
- 2) To ensure that subjects with increased inflammatory burden (i.e. high CRP) receive adequate doses of secukinumab as there is indication that they may require >75 mg.
- 3) To assess in a sufficient subject population if subjects with increased body weight require higher doses than 75 mg of secukinumab.

4) To assess the effect of secukinumab on structural benefit of the two proposed doses to see if there is a differential between these doses on this endpoint (to date no joint structure data is available for secukinumab).

5) The availability of longer term safety data for 75, 150 and 300 mg administered s.c. every 4 weeks (CAIN457F2201, CAIN457C2303).

### **3.4 Rationale for choice of comparator**

A placebo arm up to the primary endpoint at Week 24 is included in this study. Due to the nature of the disease and the outcome measures used (ACR20 criteria) a placebo arm is necessary to obtain reliable efficacy measurements. The continuation of the placebo group up to the primary endpoint at Week 24 can be supported from an ethical standpoint. Moreover the inclusion of a placebo group is in accordance with health authority guidelines, including ([FDA 1999/EMA 2003](#)).

### **3.5 Purpose and timing of interim analyses/design adaptations**

An interim analysis will be performed after all subjects have completed Week 52. The investigators, site personnel and monitors will continue to remain blinded to the treatment each subject received until the end of the trial. The X-Ray and MRI interpretation will be performed by an imaging service provider and readers will be blinded to the treatment as well as visit information.

## **4 Population**

The study population will consist of a representative group of RF and anti-CCP negative subjects at least 18 years of age, fulfilling the CASPAR criteria (see [Appendix 2](#)) and must have active PsA. Subjects included must have active disease despite current or previous NSAID, DMARD and / or TNF $\alpha$  inhibitor therapy.

Concomitant therapy with MTX ( $\leq 25$  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 must have signs of skin manifestations of psoriasis, defined by at least one psoriatic plaque of  $\geq 2$  cm diameter (but not in armpits, or chest between breasts, or groin) or nail changes consistent with psoriasis or a documented history of plaque psoriasis.

This is a multinational study and it is expected that subjects will be enrolled at approximately 150 sites. About 750 subjects will be screened for approximately 600 subjects to be randomized).

A screening failure rate of 30 % and post-randomization drop out rates of 20% at 1 year and 25% at 2 years are anticipated. Enrollment will stop as soon as the target number of randomized subjects is reached.

Subjects may only be re-screened once.

### **4.1 Inclusion criteria**

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



1. Subject must be able to understand and communicate with the investigator and be able to 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 (see [Appendix 2](#)) and with symptoms for at least 6 months with moderate to severe PsA who must have **at Baseline**  $\geq 3$  tender joints out of 78 and  $\geq 3$  swollen joints out of 76 (dactylitis of a digit counts as one joint each)
4. RF and anti-CCP antibodies negative
5. Diagnosis of active plaque psoriasis, with at least one psoriatic plaque of  $\geq 2$  cm diameter (but not in intertriginous areas such as armpits, or chest between breasts, or groin) or nail changes consistent with psoriasis or a documented history of plaque psoriasis
6. Subjects with PsA should have been on NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or intolerant to NSAIDs
7. 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 24
8. Subjects taking corticosteroids must be on a stable dose of  $\leq 10$  mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 24
9. Subjects taking MTX ( $\leq 25$  mg/week) are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization and should remain on a stable dose throughout the study
10. Subjects on MTX must be on folic acid supplementation at randomization
11. Subjects who are on a DMARD other than MTX must discontinue the DMARD 28 days prior randomization 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 $\alpha$  inhibitor must have experienced an inadequate response to previous or current treatment with a TNF $\alpha$  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 $\alpha$  inhibitor
13. Subjects who have previously been treated TNF $\alpha$  inhibitors (investigational or approved) will be allowed entry into study after appropriate wash-out period prior to randomization:
  - a. 4 weeks for Enbrel® (etanercept) – with a terminal half-life of  $102 \pm 30$  hours (s.c. route)
  - b. 8 weeks or longer for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion)
  - c. 10 weeks or longer for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route)
  - d. 10 weeks or longer for Simponi® (golimumab) – with a terminal half-life of 11-14 days

- e. 10 weeks or longer for Cimzia<sup>®</sup> (certolizumab) – with a terminal half-life of approx. 14 days

## 4.2 Exclusion criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Subjects taking high potency opioid analgesics (e.g., methadone, hydromorphone, or morphine)
2. Subjects who have ever received biologic immunomodulating agents except for those targeting TNF $\alpha$ , investigational or approved
3. Subjects who have previously been treated with more than 3 different TNF $\alpha$  inhibitors (investigational or approved)
4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor
5. Use of any investigational drug and/or devices within 4 weeks of randomization or 5 half-lives of the investigational drug, whichever is longer
6. 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 treatments (except in face, scalp and genital area during screening, only corticosteroids with mild to moderate potency) 2 weeks
6. Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization
7. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization
8. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 and investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
9. 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
10. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for 16 weeks after stopping treatment. Effective contraception is defined as either:
  - a. Barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicides (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:

- b. 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]
- c. 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
- d. Male partner sterilization. [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject]
- e. Use of established oral, injected or implanted hormonal methods of contraception, intrauterine device (IUD) or intrauterine system (IUS)

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

- 12. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy as judged by the investigator
- 13. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, infectious or gastrointestinal conditions or the management thereof which in the opinion of the investigator places the subject at unacceptable risk for participation in an immunomodulatory therapy
- 14. Significant medical diseases / problems, including but not limited to the following: Uncontrolled hypertension ( $\geq 160/95$  mmHg), congestive heart failure [New York Heart Association status of class III or IV], uncontrolled diabetes, or very poor functional status unable to perform self care
- 15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:
  - a. Any single parameter 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 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  $\mu\text{mol/L}$ )
- 16. History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a creatinine level exceeding 1.5 mg/dl (132.6  $\mu\text{mol/L}$ ) at screening
- 17. Screening total WBC count  $< 3,000/\mu\text{l}$ , or platelets  $< 100,000/\mu\text{l}$  or neutrophils  $< 1,500/\mu\text{l}$  or hemoglobin  $< 8.5$  g/dl (85 g/L)
- 18. Active systemic infections during the last two weeks (exception: common cold) prior to randomization
- 19. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis 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  $\geq 5$  mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test as indicated in the assessment schedule (see Table 6-1). 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

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

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

## 5 Treatment

### 5.1 Investigational and control treatment

The appearance of the lyophilized cake for secukinumab 150 mg Powder for Solution is slightly different from secukinumab placebo to 150 mg Powder for Solution. Also, the caps for the vials of secukinumab 150 mg powder and secukinumab placebo are different colors. Therefore, in order to maintain the blind in the study, an unblinded pharmacist or unblinded qualified site personnel will be appointed at site to prepare the study treatment.

Novartis will supply the following study treatments:

Novartis will supply the following study treatments:

- Investigational Treatment: Secukinumab  
Secukinumab 150 mg Powder for Solution for s.c. injection or i.v. infusion is provided in glass vials each containing 150 mg secukinumab as lyophilized cake. Secukinumab

150 mg vials are labeled as AIN457 150 mg. The vials contain a 20% overfill to allow a complete withdrawal of the labeled amount of secukinumab. The 150 mg Powder for Solution is used to prepare both the 75 mg and the 150 mg dose.

- **Reference Therapy: Secukinumab placebo (for s.c. injection):**  
Secukinumab placebo to 150 mg Powder for Solution for s.c. injection is provided in glass vials as lyophilized cake. Secukinumab placebo vials are labeled as AIN457 placebo. Each vial contains a mixture of inactive excipients, matching the composition of the secukinumab 150 mg Powder for Solution.

Reference therapy (Secukinumab placebo for i.v. infusion): 100 mL 0.9% NaCl solution is to be used as placebo for i.v. secukinumab, and is to be provided locally.

The supply will be open label.

For detailed instructions for storage, handling, reconstitution and administration of all study treatments, please refer to the pharmacist manual.

## 5.2 Treatment arms

At baseline, eligible subjects will be randomized to one of the following 3 treatment arms in a ratio of 1:1:1:

- **Group 1:** Secukinumab i.v. (10 mg/kg) at BSL, Weeks 2 and 4, then secukinumab 75 mg s.c. starting at Week 8 and injected every 4 weeks
- **Group 2:** Secukinumab i.v. (10 mg/kg) at BSL, Weeks 2 and 4, then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks
- **Group 3:** Placebo i.v. at BSL, Weeks 2 and 4, then placebo s.c. starting at Week 8 and Week 12.

**At Week 16 (Visit 8)**, subjects will be classified as responders ( $\geq 20\%$  improvement from baseline in both tender and swollen joint counts) or non-responders. Subjects who were randomized to placebo at baseline will be re-randomized by the Interactive Response Technology (IRT) to receive double blind treatment up to two years, as follows (see [Figure 3-1](#)):

- Subjects on placebo (Group 3) who are responders will be re-randomized (1:1) to receive either secukinumab 75 or 150 mg every 4 weeks, regardless of responder status.
- Subjects on placebo (Group 3) who are non-responders will be re-randomized (1:1) at Week 16 to receive either secukinumab 75 mg or 150 mg s.c. every 4 weeks.

## 5.3 Treatment assignment

At baseline (Visit 2), all eligible subjects will be randomized via the Interactive Response Technology (IRT) to one of the treatment arms. The IRT can be contacted via the Interactive Voice Response System (IVRS) or interactive web response system (IWRS). The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion criteria and does not fulfill any exclusion criterion. 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 unique medication numbers for the first packages of study treatment to be prepared for the subject. The unique medication number will be communicated to the

unblinded pharmacist or unblinded qualified site personnel. The randomization number will not be communicated to any of the site staff including the unblinded pharmacist or unblinded qualified site personnel. However, the unblinded pharmacist/unblinded qualified site personnel will know what treatment the subject is receiving due to the open-label packaging of the study treatments and the fact that he/she will prepare the study medication to be administered to the subject by the blinded site personnel.

At Visit 8 (Week 16), the IRT will also ask for the subject's responder status (responder/non-responder). The IRT will not generate the medication number of the vial(s) to be administered for Week 16 if the subject's responder status is missing. IRT will only communicate to the caller the medication numbers, not the randomization number.

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 Drug Supply Management using a validated system that automates the sequential assignment of medication numbers to study treatment packs containing each of the study treatments.

Randomization will be stratified according to being either TNF $\alpha$  IR or TNF $\alpha$  inhibitor naïve subjects. 30% of subjects should be TNF $\alpha$  inhibitor IR to ensure a representative subject population for the assessment of efficacy and safety. It is planned to randomize approximately 180 TNF $\alpha$  inhibitor IR subjects and 420 TNF $\alpha$  inhibitor naïve subjects.

The randomization scheme for subjects will be reviewed and approved by a member of the Novartis Audit Readiness, Validation and Randomization Group within IIS IA&R (Integrated Information Science Integrated Analytics and Reporting).

## **5.4 Treatment blinding**

This is a double-blind, randomized treatment trial. Subjects, investigator staff (with the exception of the unblinded pharmacist), persons performing the assessments, and data analysts will remain blinded to the identity of the treatment from the time of randomization until 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, the Novartis unblinded monitors and for the preparation of the study medication, an independent, unblinded pharmacist/nurse/physician or authorized personnel at the investigator's site who will prepare the study medication for subjects. (2) The identity of the secukinumab/placebo treatments will be concealed by the use of study treatments in form of syringes or i.v. infusion bags filled with reconstituted secukinumab/placebo solutions that are identical in appearance, but the actual secukinumab or placebo vials with lyophilisate will be supplied "open-label."

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

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

Whenever needed or requested by the clinical team, the bioanalyst will share information from PK measurements before clinical database lock in a blinded fashion with the pharmacokineticist.

The independent, unblinded pharmacist/nurse/physician or authorized personnel will contact the IRT after randomization to receive the treatment assignment information. He/she will then prepare the study treatment. The independent, unblinded pharmacist/nurse/physician or authorized personnel will contact the IRT again at each visit between V4 and V29 to get the treatment assignment information for the subject.

The X-Ray and MRI interpretations performed by central Imaging CRO personnel will not be disclosed to investigators, site personnel, subjects and monitors during the trial.

An interim analysis will be performed at Week 52. A selected Novartis clinical team will be unblinded to the Week 52 results. Summary results may be shared internally and externally, however individual unblinded subject data will not be disclosed. A final database lock will occur when all subjects have completed the study.

Unblinding will only occur in the case of subject emergencies (see [Section 5.5.10](#)).

## **5.5 Treating the subject**

### **5.5.1 Subject numbering**

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

Subjects who are re-screened will keep their originally assigned subject number in all systems. Subjects can only be re-screened once.

### **5.5.2 Dispensing the study treatment**

At each visit that drug is dispensed, an independent, unblinded pharmacist/nurse/physician or authorized personnel will identify the study treatment vials to administer to the subject by interacting with the IRT and obtaining the medication numbers for the s.c. injection or infusion. The unblinded pharmacist/nurse/physician or authorized personnel may contact the IRT to review the treatment assignment of a subject at any time.

Immediately before preparing the drug for administration to the subject, the unblinded pharmacist/nurse/physician or authorized personnel will document which drug has been prepared in the source documents, Pharmacist Log, Drug Preparation Form for Unblinded Personnel, Pharmacist Drug Dispensing Form, containing that subject's unique subject number.

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to a vial to be used (active or placebo). Immediately before preparation of the study medication, the unblinded pharmacist/nurse/physician or authorized site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

### **5.5.3 Supply, storage and tracking of study treatment**

Study treatment will be supplied to each study site by Novartis as open labeled bulk medication.

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 unblinded pharmacist/nurse/physician or authorized personnel has access. Upon receipt, all study treatment should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed and administered only in accordance with the protocol.

Secukinumab lyophilisate (150 mg active/placebo) must be stored in a locked refrigerator at 2-8°C and must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

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

The unblinded pharmacist/nurse/physician or authorized personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial.

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

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

### **5.5.4 Instructions for prescribing and taking study treatment**

Study treatment will be administered s.c. or by i.v. infusion throughout the study. Dose levels of 10 mg/kg for i.v. and either 75 mg or 150 mg s.c. of secukinumab or placebo will be administered.

Before administration to the subject, the study medication will have to be prepared by an unblinded pharmacist/nurse/physician or authorized site personnel appointed at the study site.



The syringes or infusion bags with the ready-to-use study medication solution prepared will be provided by the unblinded pharmacist/nurse/physician or authorized personnel to the investigator or assigned site staff, who will inject or infuse the subject during the study visit.

Detailed instructions on the preparation and administration of the study treatment will be described in the Pharmacist Manual and provided to each site.

Dosing should occur in the morning in order to coordinate sample collection times for PK assessments (see [Section 6.6.3](#)). Subjects should remain at the study site for observation for 1 hour following study treatment administration.

The first study treatment administration will occur at BSL (Visit 2) after all study scheduled assessments have been performed (and inclusion/exclusion criteria confirmed) and only after the scheduled blood samples have been drawn.

At BSL, Week 2 and Week 4 subjects will receive study medication i.v. starting at Week 8 subjects will receive study medication as s.c. injections every 4 weeks.

At study visits when pre-dose blood samples have to be drawn ([Table 6-1](#)), the study medication will be injected to the subject only after the blood samples have been taken.

At Week 1 (Visit3), Week 104 (visit 30) and during the follow-up period (Visit F112), no study treatment will be administered.

All study treatments assigned to the subject during the study will be recorded in the IRT.

The subject should be instructed to contact the investigator if he/she is unable for any reason to attend the study visit as scheduled.

All dates and times of injections and infusions administered to the subject during the study must be recorded on the Dosage administration record eCRF. All injections and infusions prepared by the pharmacist should be documented in the Source Documents for Pharmacy Drug Handling.

#### **5.5.4.1 Preparation of secukinumab solution and secukinumab placebo solution for s.c. injection or infusion**

The vials containing the lyophilisate will be appropriately diluted in order to attain the correct dosage. For full details, refer to the Pharmacist Manual.

#### **5.5.4.2 Administration**

##### **For i.v. administration**

Secukinumab active/placebo should be administered i.v. using only the materials (infusion bags, infusion lines and in-line filter) specified in writing by the sponsor and as outlined in the pharmacist manual.

The entire diluted secukinumab solution in 100 mL of 0.9% NaCl solution or 100 mL of 0.9% NaCl solution for placebo doses should be administered (please see pharmacist manual for details of administration).

### **For s.c. administration**

Secukinumab active/placebo should be administered using a 27Gx0.5`` needle (1 injection of 1 mL per visit) as outlined in the pharmacist manual.

The investigator or designee should administer the study medication by rotating body sites (thighs, arms and abdomen).

#### **5.5.4.3 After reconstitution**

From a microbiological point of view, the secukinumab Solution and secukinumab Placebo Solution for s.c. injection or for i.v. infusion, either reconstituted lyophilisate in vial, infusion bag or into the administration syringe, should be **used immediately**.

If study treatment preparation has been performed under aseptic conditions, the secukinumab Solution and secukinumab Placebo Solution for s.c. injection or for infusion might be stored at 2-8°C for no longer than 24 hours. The standing time of 24 hours is defined as the time from the first lyophilisate vial has been pierced until end of s.c. injection or infusion. If the solution is not used within 15 minutes after preparation, it should be kept at 2 - 8 °C, and allowed to come to room temperature for at least 5 to 10 minutes before administration.

Chemical and physical in-use stability of the secukinumab Solution and secukinumab Placebo Solution for s.c. injection or infusion, either reconstituted lyophilisate in vial, infusion bag or administration syringe, has been demonstrated for up to 24 hours at 2 to 8°C.

Any unused product or waste material should be disposed of in accordance with local requirements.

#### **5.5.5 Permitted dose adjustments and interruptions of study treatment**

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

Study treatment interruption is permitted if a subject in the opinion of the investigator develops a serious infection. In such a case study treatment must be interrupted until the infection is controlled. Study treatment can be started again at the next scheduled visit after resolution of the infection at the discretion of the investigator regardless of concomitant antibiotic treatment.

Study treatment may also be temporarily interrupted for surgical procedures but only in consultation with the Novartis study team.

Live vaccines must not be administered during the first 24 weeks of participation in the study. After Week 24 live vaccines should also not be administered until 12 weeks after the last dose of study treatment. In case a live vaccine has been administered due to a medical urgency after completion of 24 weeks, study treatment should be interrupted for at least 12 weeks.

Any study treatment interruption must be recorded on the corresponding eCRF(s).

#### **5.5.6 Rescue treatment**

Rescue medication must not be used before completion of Visit 10 (Week 24). Please see [Sections 5.5.7](#) and [Section 5.5.8](#) for details.

Any use of rescue medication must be recorded on the corresponding Concomitant Medications eCRF.

### **5.5.7 Concomitant treatment**

The investigator should instruct the subject to notify the study site about any new medications (including over-the-counter drugs, calcium and vitamins) he/she takes after the start of the study treatment. All medications (other than study treatment) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject starts treatment with study treatment must be listed on the corresponding eCRF. The reason and the name of the drug should be listed.

Guidelines for the use of specific medications are provided below:

#### **Methotrexate**

Subjects on MTX have to be treated with stable treatment of MTX ( $\leq 25$  mg/week) for at least 4 weeks before randomization and maintained stable throughout the treatment period.

#### **Folic acid**

Subjects on MTX must be taking folic acid supplementation before randomization and during the trial to minimize the likelihood of MTX associated toxicity. Folic acid supplementation should not be taken on the same day than MTX intake.

#### **Leflunomide wash-out with cholestyramine**

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

#### **Systemic corticosteroids**

Treatment with systemic corticosteroids will be allowed if the dose was stable for at least 4 weeks before randomization and maintained stable throughout the study period. A maximum dosage of 10 mg equivalent of daily prednisone will be allowed.

Corticosteroid dose reductions are permitted after Week 16. However, for any dose reductions after Week 16, the corticosteroid dose should not be reduced more than 1 mg prednisone equivalent every 4 weeks.

Intra-articular corticosteroids are not permitted within 4 weeks prior to baseline and up to week 24. After week 24, 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 steroids is not permitted within 8 weeks prior to Weeks 24, 52, and 104.

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

### **Non-steroidal anti-inflammatory drugs (NSAIDs) (COX-1 or 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 4 weeks before randomization to allow inclusion and during the treatment period.

Subjects taking NSAIDs, low strength opioids, or paracetamol/acetaminophen PRN within the 4 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.

However, any change of the NSAIDs, opioids, or paracetamol/acetaminophen treatment during the trial should be recorded on the corresponding eCRF.

### **5.5.8 Prohibited treatment**

Use of the treatments listed in [Table 5-1](#) is NOT allowed after the start of the washout period.

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

**Table 5-1 Prohibited treatment**

<b>Prohibited treatments</b>	<b>Washout period (before randomization)</b>
Biological immunomodulating agents $\geq$ 3 different TNF $\alpha$ inhibitors	Never
Etanercept	4 weeks
Infliximab	8 weeks
Adalimumab, golimumab, certolizumab	10 weeks
Unstable dose of MTX	4 weeks
Other DMARD (except MTX)	4 weeks
Leflunomide	8 weeks
Leflunomide with Cholestyramine washout	4 weeks
Unstable dose of NSAIDs (COX1 or COX2 inhibitors)	4 weeks
Systemic corticosteroids $\geq$ 10 mg prednisone equivalent	4 weeks
Intra-articular steroid injections up to Week 24	4 weeks
Oral or topical retinoids	4 weeks
Photochemotherapy (e.g. PUVA)	4 weeks

<b>Prohibited treatments</b>	<b>Washout period (before randomization)</b>
Phototherapy (UVA or UVB)	2 weeks
Topical treatments (except in face, scalp and genital area during screening, only corticosteroids with mild to moderate potency)	2 weeks
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Analgesics other than paracetamol/acetaminophen and low strength opioids PRN	4 weeks
Live vaccinations up to Week 24	6 weeks

### 5.5.9 Discontinuation of study treatment and premature subject withdrawal

Study treatment must be discontinued and the subject withdrawn from the trial if the investigator determines that continuing it would result in a significant safety risk for that subject. The following circumstances **require** study treatment discontinuation:

- Withdrawal of informed consent
- Emergence of the following adverse events:
  - Any severe or serious adverse event that is not compatible with administration of study treatment, including adverse events that require treatment with an unacceptable co-medication up to Week 24
  - 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.
  - Life threatening infection
- Administration of a live vaccine up to Week 24
- Any of the following laboratory abnormalities (based on recommendations by CTEP (Cancer Therapy Evaluation Program, National Institute of Health)):
  - AST or ALT value  $>5$  x ULN  
**Note:** For an AST or ALT value between  $>3$  x ULN and  $\leq 5$  x ULN, the test should be repeated within 2 weeks. Subjects with a value greater than or equal to the previous one at repeat testing should be discontinued.
  - Hemoglobin value  $<85$  g/L (8.5 g/dL) and decreased by at least 20 g/L (2 g/dL) from screening
  - Creatinine value  $>2$  x ULN
- Pregnancy
- Use of the following medication(s):
  - Any biologic immunomodulating agent except secukinumab

- Any other protocol deviation that results in a significant risk to the subject's safety

In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator.

In addition to these requirements for study treatment discontinuation, the investigator should discontinue study treatment for a given subject if, on balance, he/she thinks that continuation would be detrimental to the subject's well-being.

Subjects who discontinue study treatment should not be considered withdrawn from the study. A Study treatment Discontinuation form should be completed, giving the date and primary reason for stopping study treatment. For subjects remaining in the trial, all Week 52 assessments must be performed on the day of study treatment discontinuation or as early as possible after study treatment discontinuation; all subsequent visits will be performed according to the assessment schedule (Table 6-1).

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

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

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

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a subject's premature withdrawal from the study and record this information on the Study completion eCRF.

The investigator should ensure that the subject returns for an end of study visit (week 104) 4 weeks after last study treatment, and a follow-up visit (F112) 12 weeks after last study treatment. Even if the subject is not willing to come back for all assessments, every effort should be made to collect the scheduled X-ray assessments.

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

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

#### **5.5.10 Emergency unblinding of treatment assignment**

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. 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 code breaks are performed using the IRT. When the investigator contacts the system to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. The investigator will then receive details of the study 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 Clinical Trial Head that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study treatment name if available, subject number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the subject in case emergency unblinding is required at a time when the investigator and backup are unavailable.

Study treatment must be discontinued after emergency unblinding.

### **5.5.11 Study completion and post-study treatment**

A subject will be considered to have completed the study if he/she received a maximum of 100 weeks of study treatment and upon completion of all the scheduled study assessments and procedures up to and including Week 112.

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.

Study Completion evaluations must also be performed when a subject prematurely withdraws from the study for whatever reason.

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 is recommended before initiating the treatment.

### **5.5.12 Early study termination**

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the subject should be seen as soon as possible and treated as described in [Section 6](#) for 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 will be responsible for informing IRBs and/or ECs of the early termination of the trial.

## **6 Visit schedule and assessments**

[Table 6-1](#) lists all of the assessments and indicates with an "X" the visits when they are performed.

Subjects should be seen for all visits on the designated day or as closely as possible to the original planned visit schedule. For all infusion visits (Visits 2, 4 and 5), study treatment should not be administered within less than 1 week after the previous infusion. Starting at Visit 6 (Week 8), subjects should not receive study treatment within less than 2 weeks after the previous administration.

**Table 6-1 Assessment schedule**

	SCR	Treatment Period 1																Treatment Period 2														Follow-up
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	F112 <sup>8</sup>	
Week	≤-4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104 <sup>13</sup> / Disc. Subj.	112	
Informed consent / optional PG informed consent	X																															
Inclusion/Exclusion criteria	X	X																														
Relevant medical history/ current medical condition	X																															
Cardiovascular medical history		X																														
Psoriasis/psoriatic arthritis medical history and previous psoriasis/psoriatic arthritis therapies	X	X																														
Smoking history		X																														
Demography	X																															
Physical Exam <sup>1</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X																															
Weight	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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PPD skin test <sup>2</sup> or QuantiFERON TB-Gold test	X																															
Rheumatoid factor (RF)	X																															
Anti-CCP antibodies	X									X						X														X		
Chest X-ray <sup>3</sup>	X																															
ECG (central)		X						X								X														X		
Randomization		X						X <sup>4</sup>		X <sup>4</sup>																						



	SCR	Treatment Period 1																Treatment Period 2										Follow-up			
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	F112 <sup>8</sup>
Week	≤-4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104 <sup>13</sup> / Disc. Subj.	112
Administration of i.v. study treatment		X		X	X																										
Administration of s.c. study treatment						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior medication	X	X																													
Hematology, blood chemistry, local urinalysis	X	X	X	X	X	X	X	X	X	X	X	X		X			X		X		X		X		X		X		X	X	X
Serum pregnancy test	X																														
Urine pregnancy test		X			X		X	X		X		X		X		X		X		X		X		X		X		X		X	X
Con medication/non drug therapy	Update as necessary throughout the study																														
Adverse Events/SAE <sup>5</sup> (including injection site reaction & infections)	Update as necessary throughout the study																														
MRI (swollen hand/wrist; TNF-naïve subjects only) <sup>12</sup>		X					X			X																					
X-Ray (hands/wrists + feet) <sup>6</sup>		X						X <sup>9</sup>		X <sup>10</sup>						X														X <sup>11</sup>	
ANA		X								X						X														X	
Anti-dsDNA		X								X						X														X	
Immunogenicity		X								X						X														X	X
PK assessments (at predose)		X			X		X		X		X					X													X	X	
Tender & Swollen joint counts (TSJ78 / SJC76)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's assessment of PsA pain (VAS scale)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's global assessment of disease activity (VAS scale)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	SCR	Treatment Period 1															Treatment Period 2										Follow-up				
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	F112 <sup>8</sup>
Week	≤-4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104 <sup>13</sup> / Disc. Subj.	112
Physician's global assessment of disease activity (VAS scale)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X			X	
Health Assessment Questionnaire (HAQ-DI)		X	X	X	X	X	X	X	X	X	X	X	X	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	X		X		X		X		X		X			X	X
Erythrocyte Sedimentation Rate (ESR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X			X	X
Leeds Dactylitis Index	X	X		X	X	X	X	X		X		X		X			X		X		X		X		X		X			X	
Leeds Enthesitis Index	X	X		X	X	X	X	X		X		X		X			X		X		X		X		X		X			X	
PASI (only if > 3% of BSA at BSL)		X	X	X	X	X	X	X		X		X		X			X		X		X		X		X		X			X	
IGA (only if > 3% of BSA at BSL)		X	X	X	X	X	X	X		X		X		X			X		X		X		X		X		X			X	
Target Lesion Score (TLS; only if target lesion with > 2cm diameter)		X	X	X	X	X	X	X		X		X		X			X		X		X		X		X		X			X	
mNAPSI (only in patients with nail involvement)		X	X	X	X	X	X	X		X		X		X			X		X		X		X		X		X			X	
WPAI-GH v2		X						X		X							X													X	
SF-36 Acute Form v2		X			X	X	X	X		X							X													X	
FACIT-Fatigue v4		X			X	X	X	X		X							X													X	
PsAQoL		X			X	X	X	X		X							X													X	
EQ-5D v3L		X			X	X	X	X		X							X													X	
DLQI (only if > 3% of BSA at BSL)		X			X	X	X	X		X							X													X	
Lipids <sup>6</sup>		X				X		X		X							X							X						X	
Cardiovascular panel		X						X		X							X													X	
Serum biomarkers related to targeted pathway		X								X							X													X	

	SCR	Treatment Period 1															Treatment Period 2										Follow-up				
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	F112 <sup>8</sup>
Week	≤4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104 <sup>13</sup> / Disc. Subj.	112
Pharmacogenetics <sup>7</sup>		X																													
Treatment Period 1 Completion Form																	X														
Treatment Period 2 Completion Form																														X	
Follow-up period Completion Form																															X

<sup>1</sup>These assessments are source documentation only and will not be entered into the eCRF

<sup>2</sup> The PPD skin test can be performed at any time during the screening period but it has to be read within 72 hrs and before randomization

<sup>3</sup> A chest X-ray is required if it was not performed and evaluated within 3 months before screening

<sup>4</sup> Subjects will be re-assigned/re-randomized new treatment according to their response and to the treatment they were randomized to at visit 2

<sup>5</sup> AEs/SAEs occurring after the subject has provided informed consent must be reported

<sup>6</sup> Samples must be obtained fasting

<sup>7</sup> Pharmacogenetic sample should only be collected after separate Informed Consent Form (ICF) is signed

<sup>8</sup> Follow-up visit to be done 12 weeks after last study treatment administration for subjects who terminated the study early or for subjects who completed the study but do not enter the extension study

<sup>9</sup> X-rays only taken for subjects who are non-responder at Week 16 (not achieving a 20% reduction in both, TJC and SJC)

<sup>10</sup> X-rays only taken for subjects who are responder at Week 16 (achieving a 20% reduction in both, TJC and SJC)

<sup>11</sup> Subjects who discontinue will have their X-rays taken only if more than 60 days have elapsed since their last X-rays

<sup>12</sup> Subjects who undergo the MRI assessments need to be TNFα inhibitor naïve and should have a swollen wrist at baseline; the more swollen wrist should be scanned; if both hands are equally swollen, the dominant hand should be scanned

<sup>13</sup> In case of premature discontinuation, assessments to be done as soon as possible

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## 6.1 Information to be collected on screening failures

Subjects may discontinue from the study prior to. Those subjects 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 Screening Phase Disposition eCRF. In addition only the following eCRFs should be completed: Demography eCRF, Informed Consent eCRF, Inclusion/Exclusion eCRF, and the AE eCRF should be completed for any SAEs that occurred during the screening period.

## 6.2 Demographics/other baseline characteristics

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

- Date of birth, 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 TNF $\alpha$  inhibitor naïve or IR, cardiovascular medical history, and smoking history

Whenever possible, diagnoses and not symptoms will be recorded.

## 6.3 Treatment exposure and compliance

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

Drugs administered prior to start of treatment and other drugs continuing or started during the study treatment period will be entered in the Prior/Concomitant medications/significant non-drug therapies eCRF. Compliance is expected to be 100% (unless temporary interruption is needed for safety reasons as described in [Section 5.5.5](#)) since study treatment will be administered by the investigator or site staff. Compliance will also be assessed by a Novartis monitor using vial counts and information provided by the unblinded pharmacist/nurse/physician or authorized site personnel

## 6.4 Efficacy

- ACR 20, 50 and 70 response (incl. Major Clinical Response)
- PsARC response
- Disease Activity Score (DAS28) and EULAR response criteria
- HAQ-DI<sup>®</sup>
- Leeds Enthesitis Index (LEI)
- Leeds Dactylitis Index (LDI)
- Progression of structural damage by X-ray (hands/wrists and feet) – van der Heijde modified total Sharp score and subscores (erosion and joint space narrowing score)

- MRI of hand/wrist (in a subgroup of TNF $\alpha$  inhibitor naïve subjects at selected clinical sites only)
- Psoriasis Area and Severity Index (PASI)
- IGA (mod 2011)
- Target lesion Score
- Modified Nail Psoriasis Severity Index (mNAPSI)
- Swollen Joint Count (SJC)/Tender Joint Count (TJC)
- Patient's assessment of pain intensity (VAS scale)
- Patient's global assessment of disease activity (VAS scale)
- Physician's global assessment of disease activity (VAS scale)
- Erythrocyte Sedimentation Rate (ESR) and high sensitivity C-Reactive Protein (hsCRP)

#### **6.4.1 American College of Rheumatology (ACR) response**

The primary efficacy variable is the clinical response to treatment according to ACR20 individual improvement in disease activity at Week 24. A subject is defined as an ACR20 responder if, and only if, the following three conditions hold (See [Appendix 3](#)):

1. they have a  $\geq 20\%$  improvement in the number of tender joints (based on 78 joints)
2. they have a  $\geq 20\%$  improvement in the number of swollen joints (based on 76 joints)
3. they have a  $\geq 20\%$  improvement in three of the following five domains
  - Patient Global Assessment (measured on a VAS scale, 0-100)
  - Physician Global Assessment (measured on a VAS scale, 0-100)
  - Patient's assessment of PsA pain (measured on a VAS scale, 0-100)
  - Disability (HAQ-DI<sup>®</sup> score)
  - Acute phase reactant (hsCRP or ESR)

Additionally, Major Clinical Response (continuous six-month period of ACR70 response) will be assessed as a key secondary objective at week 52

##### **6.4.1.1 Tender 78 joint count and swollen 76 joint count**

Joint counts will be performed at scheduled visits as indicated in [Table 6-1](#), by the independent assessor(s) who must be well trained and part of the site personnel. Whenever possible, the same evaluator should perform these assessments at all visits.

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

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

#### **6.4.1.2 Patient's assessment of PsA pain intensity**

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

#### **6.4.1.3 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*".

#### **6.4.1.4 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 patient.

#### **6.4.1.5 HAQ-DI**

The HAQ-DI is a key secondary efficacy endpoint for this study. The HAQ-DI<sup>®</sup> 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.

Patient reported outcomes (PROs) will be collected using the digital pen technology. Details relating to the administration of all PROs are provided in [Appendix 9](#).

#### **6.4.1.6 High Sensitivity C-reactive protein (hsCRP)**

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

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

#### **6.4.1.7 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 (see [Table 6-1](#)).

#### **6.4.2 DAS28 and EULAR response**

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

#### **6.4.3 PsARC response**

A subject is defined as a PsARC responder if, and only if, they have an improvement in two of the following four factors (with at least one factor being a joint count) and no worsening in the remaining factors

- Patient global assessment (0-100 mm VAS scale, improvement defined as decrease of at least 20 mm)
- Physician global assessment (0-100 mm VAS scale, improvement defined as decrease of at least 20 mm)
- Tender 78-joint count (improvement defined as decrease of at least 30%)
- Swollen 76-joint count (improvement defined as decrease of at least 30%)

#### **6.4.4 Radiographic assessments**

Separate radiographs of each hand/wrist (PA) and each foot (AP) will be taken at baseline, Week 24, 52, and 104. Bone erosion, joint space narrowing (JSN), and total radiographic scores will be determined using a PsA modified van der Heijde-Sharp (vdH-S) scoring method ([van der Heijde 2005](#)) that includes the second through fifth distal interphalangeal (DIP) joints of each hand. Erosions (0–5 in the hands and 0–10 in the feet) and JSN (0–4) will be graded separately in six wrist joints, all metacarpal phalangeal, proximal interphalangeal, and DIP joints of each hand, and the first interphalangeal joint and all metatarsal phalangeal joints for each foot. The total radiographic score (hands and feet combined) ranges from 0 to 528, with higher scores indicating more articular damage. The maximum total erosion score is 360. The maximum total JSN score is 168.

The change in the Van der Heijde modified Sharp score is calculated against the baseline value. Radiologists will be trained on the X-ray acquisition and further details will be provided in a manual for the radiologists, e.g. joint placement and beam positioning.

In case of analogue X-rays films, the original film will be sent to the central reading CRO and will undergo quality control and will be digitized. Standard film and cassettes will be provided to all centers that do not produce digital X-rays. In case of digital equipment, sites need to confirm minimum requirements with the imaging CROs. Digital X-rays will be transferred electronically.

In case of insufficient quality, the center will be advised and trained on any quality issues prior to the repeat X-ray and to keep any repeat X-rays to a minimum.

Subjects who are non-responder at Week 16 (not achieving a  $\geq 20\%$  improvement from baseline in both TJC and SJC) will have their hands/wrists and feet X-rays taken at this visit (Week 16). Subjects who are responder at Week 16 ( $\geq 20\%$  improvement from baseline in both tender and swollen joint counts) will have their hands/wrists and feet X-rays taken at Week 24. Subjects who discontinue study treatment before the end of the trial, hands/wrists and feet X-rays will be taken at the time of study treatment discontinuation. However, if the radiograph performed at time of early discontinuation of study treatment is less than 60 days to a prior X-ray, it does not need to be performed. Likewise, if a scheduled X-ray at Week 24, 52, or 104 is scheduled less than 60 days after any prior hands/wrists and feet X-rays, it does not need to be performed. All following X-rays will be performed as scheduled.

The readings of the X-rays and the scoring will be performed centrally. Complete X-ray procedures will be defined in an Imaging Manual provided to the centers by an Imaging CRO designated by Novartis.

#### **6.4.5 Magnetic Resonance Imaging (MRI)**

MRI will be performed in a subgroup of approximately 90 subjects with at least one swollen wrist at baseline (approx. 30 subjects/treatment arm) at selected sites. The hand with the more swollen wrist should be chosen (determined at baseline by the investigator). If both wrists are equally affected, the dominant hand/wrist should be chosen. The site should ensure that the same hand/wrist selected at baseline will be scanned at the following visits. Subjects with any contraindications to MRI (e.g.: pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments, foreign objects in the eyes, skin or body or severe claustrophobia) or to gadolinium injections (e.g. allergic or adverse reactions to gadolinium, estimated glomerular filtration rate below 60 mL/1.73 m<sup>2</sup> (based on MRD formula)) should not perform an MRI evaluation.

MRIs will be performed at BSL, Week 12 and Week 24 using a whole body MRI system. The MRI assessment will require gadolinium contrast agent injections. MRI machines should have a field strength of 1.5 Tesla. The MRI protocol and required sequences will be described in the imaging acquisition manual.

The readings of the scan and the scoring will be performed centrally. Readers will be blinded to clinical information and to the sequence of the images. The MRIs will be scored according to a modified OMERACT RAMRIS system ([Ostergaard 2010](#)) for erosions, bone marrow edema (BME), and synovitis. In addition, JSN will be scored ([Peterfy 2010](#)).



### 6.4.6 Psoriasis Area and Severity Index (PASI)

The PASI assessment will be conducted for subjects in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at baseline (Visit 2). The PASI assesses the extent of psoriasis on four body surface areas (head, trunk and upper and lower limbs) and the degree of plaque erythema, scaling and thickness. A PASI score (Fredriksson and Pettersson 1978, Weisman 2003, Gottlieb 2005) will be derived as indicated in Table 6-2. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

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

**Table 6-2 The PASI scoring system**

Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation) (D)	Area score (based on true area %, A)*
Head (H)**	0=none	0=none	0=none	0 = 0%
	1=slight	1=slight	1=slight	1 = 1-9%
	2=moderate	2=moderate	2=moderate	2 = 10-29%
	3=severe	3=severe	3=severe	3 = 30-49%
	4=very severe	4=very severe	4=very severe	4 = 50-69%
				5 = 70-89%
			6 = 90-100%	
Trunk, (T)***	0=none	0=none	0=none	0 = 0%
	1=slight	1=slight	1=slight	1 = 1-9%
	2=moderate	2=moderate	2=moderate	2 = 10-29%
	3=severe	3=severe	3=severe	3 = 30-49%
	4=very severe	4=very severe	4=very severe	4 = 50-69%
				5 = 70-89%
			6 = 90-100%	
Upper limbs (U)	0=none	0=none	0=none	0 = 0%
	1=slight	1=slight	1=slight	1 = 1-9%
	2=moderate	2=moderate	2=moderate	2 = 10-29%
	3=severe	3=severe	3=severe	3 = 30-49%
	4=very severe	4=very severe	4=very severe	4 = 50-69%
				5 = 70-89%
			6 = 90-100%	
Lower	0=none	0=none	0=none	0 = 0%

Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation) (D)	Area score (based on true area %, A)*
limbs (L)****	1=slight	1=slight	1=slight	1 = 1-9%
	2=moderate	2=moderate	2=moderate	2 = 10-29%
	3=severe	3=severe	3=severe	3 = 30-49%
	4=very severe	4=very severe	4=very severe	4 = 50-69%
				5 = 70-89%
			6 = 90-100%	

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

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

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

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

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

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

The keys for the letters are provided in [Table 6-2](#).

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

#### 6.4.7 Investigator's Global Assessment (IGA mod 2011)

IGA mod 2011 will be conducted for overall psoriatic disease as indicated in [Table 6-3](#) for subjects in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at baseline (Visit 2). It is recommended that the same evaluator conducts the assessment throughout the study wherever possible.

The IGA mod 2011 rating scale for overall psoriatic disease is shown in [Table 6-3](#).

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

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

The IGA mod 2011 score will be recorded in the eCRF.

**Table 6-3 The IGA mod 2011 rating scale**

Score	Short Description	Detailed Description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present.

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1	Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling.
2	Mild	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling.
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling.
4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe / coarse scaling covering almost all or all lesions.

---

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

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

#### 6.4.8 Target lesion score (TLS)

The Target Lesion Score will be done for subjects enrolled in the study having a psoriatic target lesion that is at least 2 cm in diameter identified at baseline (Visit 2). At the visits indicated in [Table 6-1](#), this target lesion will be scored for erythema, scaling, and thickness, each on a scale of 0 to 4 (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe). The parameter scores will be summed automatically in the eCRF, giving a score ranging from 0 to 12.

#### 6.4.9 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 ([Cassel 2007](#)). More information is provided in [Appendix 7](#).

#### 6.4.10 Leeds Dactylitis Index (LDI)

The Leeds Dactylitis Index (LDI) ([Helliwell 2005](#)) basic measures the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot, using a minimum difference of 10% to define a dactylitic digit. The ratio of circumference is multiplied by a tenderness score, using a modification of LDI which is a binary score (1 for tender, 0 for non-tender). If both sides are considered involved, the number will be compared to data provided in the standard reference tables (see [Appendix 8](#)). This modification is referred to as LDI basic and will be applied in this study. The LDI requires a finger circumference gauge or a tape measure to measure digital circumference.

#### **6.4.11 Leeds Enthesitis Index (LEI)**

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

#### **6.4.12 Appropriateness of efficacy assessments**

The efficacy outcome measures used in this study are the standard measures used across many psoriatic arthritis trials and they are required for regulatory filing.

### **6.5 Safety**

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

#### **6.5.1 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 only 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.

##### **QuantiFERON TB-Gold test**

- A QuantiFERON TB-Gold test is to be performed at screening (Visit 1) 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 performed 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. 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 cleansed 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 investigators' site within that time for a proper 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  $\geq 5$  mm (or according to local practice/guidelines) is interpreted as a positive result

### **6.5.2 Physical examination**

A physical examination will be performed at each visit. Significant findings that are present before the subject has signed the Informed Consent Form must be included in the relevant medical history eCRF. Significant findings made after the subject has signed the Informed Consent Form which meet the definition of an AE must be recorded in the Adverse Event case report form. It will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems.

### **6.5.3 Vital signs**

### **6.5.4 Height and weight**

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

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

### **6.5.5 Electrocardiogram (ECG)**

A standard 12-lead ECG will be performed at visits as indicated in [Table 6-1](#).

All ECGs must be performed on the ECG machines provided for the study.

All ECGs will be independently reviewed. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG investigator manual.

Clinically relevant abnormalities should be recorded on the relevant Medical History/Current Medical Conditions eCRF for the baseline ECG.

Clinically relevant abnormalities noted after the baseline ECG should be reported as AEs (see [Section 7](#)).

### **6.5.6 Local tolerability (injection site reactions)**

The local tolerability at the site of s.c. injection will be assessed in the case of any local reaction, until this has disappeared.

The assessment of pain, redness, swelling, induration, hemorrhage and itching will be performed by a physician and will be recorded on the Adverse Event eCRF, including the severity (none, mild, moderate, severe) and the duration.

### **6.5.7 Laboratory evaluations**

A central laboratory will be used in this study. Central laboratory information, including collection, shipment of samples and reporting of results, may be found in the laboratory manual. For the identification of notable values, see [Appendix 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 drug related AE, is defined.

#### **6.5.7.1 Hematology**

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

#### **6.5.7.2 Clinical chemistry**

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

#### **6.5.7.3 Lipid panel**

A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), cholesterol and triglycerides will be measured from a fasting blood sample.

#### **6.5.7.4 Cardiovascular panel**

A cardiovascular profile including lipoprotein (a), apolipoprotein B-100, apolipoprotein A-1, and adiponectin will be measured from a blood sample.

#### **6.5.7.5 Urinalysis**

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

#### **6.5.8 Pregnancy and assessments of fertility**

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

A serum  $\beta$ -hCG test will be performed in all women at Visit 1 (screening). All women who are not surgically sterile at screening will have local urine pregnancy tests as indicated in [Table 6-1](#). A positive urine pregnancy test requires immediate interruption of study medication until serum  $\beta$ -hCG is performed and found to be negative. If positive, the subject must be discontinued from the trial.

#### **6.5.9 Tolerability of secukinumab**

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

#### **6.5.10 Additional parameters**

Blood will be obtained at Visit 1 (screening) for ANA, dsDNA, anti-CCP antibodies, and Rheumatoid Factor (RF).

### 6.5.11 Immunogenicity

Blood samples for immunogenicity (anti-secukinumab antibodies) will be taken pre-dose at the scheduled timepoints as indicated in Table 6-1. In addition, if a subject discontinues from the study at any timepoint, he/she will need to provide a sample at the last visit.

The actual sample collection date and exact time will be entered on the Immunogenicity blood collection eCRF. Sampling problems will be noted in the Comments section of the eCRF.

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

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

Tubes and preprinted labels will be provided by the central lab to the sites.

### Analytical Method

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

**Table 6-4 IG sample log**

Visit	Week	IG Sample number
2	0	301
10	24	302
17	52	303
30	104	304
F112	112	305

### 6.5.12 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic in PsA. The specific focus on infection rates in addition to the other safety measures ensures the ability to deliver data on a critical safety endpoint for this class of therapy. A Chest X-ray at screening is performed to rule out the presence of a pulmonary malignancy or infectious process, in particular tuberculosis. The radiation exposure that results from these X-ray measurements is not necessary for medical care but is intended for research purposes only. The total amount of radiation from all X-ray measurements performed in this study (1 safety chest X-ray, 3-4 X-rays of hands/wrists and feet) is estimated to be around 1 mS over 104 weeks, and is approximately equivalent to a uniform whole body exposure of 26 weeks of

exposure to natural background radiation. For effective radiation doses under 3 mSv (300 mrem), the risk is considered to be "minimal". Therefore, the radiation exposure in this study involves minimal risk and is necessary to obtain the research information desired and ensure reliable safety measures before the treatment with a biologic.

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

## 6.6 Other assessments

- Quality of Life questionnaire/ Patient reported outcomes (PROs)
- Pharmacokinetics
- Pharmacogenetics
- Serum biomarkers related to targeted pathway

### 6.6.1 Quality of Life questionnaires/Patient Reported Outcomes (PROs)

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

- HAQ-DI (see [Section 6.4.1.5](#))
- SF-36 v2 (Acute form)
- EQ-5D
- FACIT-Fatigue
- PsAQoL
- DLQI

All questionnaires will be available, where possible, in the local languages of the participating countries and should be completed by subjects before they see the study physician. The subject should be given sufficient space and time to complete the questionnaire.

Responses will be collected on digital paper to allow the use of a digital pen. Only the original digital paper provided can be used for the digital pens (i.e. these pages must not be photocopied).

All questionnaires will be completed in the respondent's local language. The study coordinator should check the questionnaires for completeness and encourage the subject to complete any missing responses. The original questionnaires will be kept with the subject's file as the source document.

Completed questionnaires should be reviewed and assessed by the investigator, before the clinical examination, for responses which may indicate potential AEs or SAEs. This assessment should be documented in the source records. If AEs or SAEs are confirmed the investigator should record the events as per instructions given in the relevant section of the protocol (see [Section 7](#)).

Guidelines for administering the PRO questionnaires can be found in [Appendix 9](#).



### 6.6.1.1 SF-36 Version 2 (Acute Form)

The Short Form Health Survey (SF-36) is a widely used and extensively studied instrument to measure health-related quality of life among healthy subjects and patients 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 (Ware 1993). Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed (Ware 1994). 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 in this study is to assess the HRQoL of subjects. Given the acute nature of this disease, version 2, with a 1-week recall period, will be used in this study.

### 6.6.1.2 EQ-5D

The EQ-5D is a widely used, self-administered questionnaire designed to assess health status in adults. The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Subjects rate each of these items from "no problem," "some problem," or "extreme problem." A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is "today," and the questionnaire requires approximately 5 to 10 minutes to complete.

The EQ-5D contains six items designed to assess health status in terms of a single index value or health utility score. One of the strengths of the EQ-5D approach is that it allows "weighting" by the subject of particular health states and the generation of subject utilities. Published weights are available that allow for the creation of a single summary health utility score. Overall scores range from 0 to 1, with lower scores representing a higher level of dysfunction.

The purpose of the EQ-5D in this study is to assess the health status of subjects.

### 6.6.1.3 FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue<sup>®</sup>) is a 13-item questionnaire (Cella 1993; Yellen 1997) that assesses self-reported fatigue and its impact upon daily activities and function.

The purpose of FACIT-Fatigue<sup>®</sup> in this study is to assess the impact of fatigue on subjects with PsA.

#### **6.4.5.1. PsAQoL**

The PsAQoL is a 20-item questionnaire designed to assess the impact of PsA and its treatment on quality of life. Each item of the questionnaire is in the form of a simple statement to which subjects indicate whether or not the statement is true for them at that moment.

The theoretical basis for the PsAQoL is the needs-based model of QoL which argues that disease-related impairment and disability influences a person's ability to meet his or her needs.

#### **6.6.1.4 DLQI**

The Dermatology Life Quality Index (DLQI) is a 10-item general dermatology disability index designed to assess health-related quality of life in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral warts (Finlay and Khan 1994). The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 32 different skin conditions and is available in multiple languages. The recall period is the past week, and the instrument requires 1 to 2 minutes for completion.

Each item has four response categories ranging from 0 (not at all) to 3 (very much). "Not relevant" is also a valid response and is scored as 0. The DLQI total score is a sum of the 10 questions. Scores range from 0 to 30, and higher scores indicate greater health-related quality of life impairment. Additionally, each subscale of the DLQI may be analyzed separately.

#### **6.6.1.5 Work Productivity and Activity Impairment (WPAI-GH)**

The Work Productivity and Activity Impairment (WPAI-GH) questionnaire is an instrument to measure impairments in both paid work and unpaid work. It measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problem during the past seven days. The WPAI-GH consists of six questions:

- 1 = currently employed
- 2 = hours missed due to health problems
- 3 = hours missed other reasons
- 4 = hours actually worked
- 5 = degree health affected productivity while working (VAS)
- 6 = degree health affected productivity in regular unpaid activities (VAS)

The recall period for the questions 2 to 6 is seven days. Four main outcomes can be generated from the WPAI-GH and expressed in percentages.

1. percent work time missed due to health for those who were currently employed
2. percent impairment while working due to health for those who were currently employed and actually worked in the past seven days
3. percent overall work impairment due to health for those who were currently employed
4. percent activity impairment due to health for all respondents

### 6.6.2 Pharmacokinetics

Pharmacokinetic (PK) samples will be obtained for all subjects, and secukinumab concentrations will be assessed in serum. The PK samples will be collected pre-dose at scheduled visits as indicated in [Table 6-1](#).

All blood samples will drawn by direct venipuncture in a forearm vein.

The actual sample collection date and exact time will be entered on the PK blood collection summary eCRF. Sampling problems will be noted in the Comments section of the eCRF.

The bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the PK samples. The bioanalyst will provide the samples' concentration data to the team under blinded conditions. Both the site's unblinded pharmacist and bioanalyst will keep this information confidential until clinical database lock.

### PK sample handling, labeling and shipment instructions

Laboratory manuals will be provided by the central laboratory with detailed information on sample collection, sample handling and shipment.

Tubes and labels will be provided by the central laboratory with study/sample type information pre-printed on the label.

**Table 6-5 PK sample log**

Visit	Week	Time	Sample number	PK collection number
2	0	0 (pre-dose)	1	1
5	4	672 h (pre-dose)	2	1
8	16	2688 h (pre-dose)	3	1
10	24	4032 h (pre-dose)	4	1
17	52	8736 h (pre-dose)	5	1
30	104	17472 h (anytime)	6	1
F112	112	18816 h (anytime)	7	1

### Analytical methods

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

### 6.6.3 Pharmacogenetics

The pharmacogenetic endpoints are exploratory and are not intended to be used for regulatory judgments pertaining to the safety or efficacy of the investigational drug. However, these data may be considered for voluntary submission, consistent with applicable regulatory guidance on this topic, in order to develop the knowledge base necessary to establish the validity of new genomic biomarkers.

This study includes an optional exploratory pharmacogenetic assessment which requires signature of a separate informed consent if the subject agrees to participate. The identity of the subject will not be revealed. It is required as part of this protocol that the Investigator presents these options to the subject.

Exploratory pharmacogenetics studies are planned as a part of this study with the objectives of identifying inherited genetic factors that may (1) be related to PsA, (2) predict response to treatment with secukinumab, (3) predict relative susceptibility to drug-drug interactions, or (4) predict genetic predisposition to side effects. We hope to develop a better understanding of PsA and how subjects respond to secukinumab.

The genetic markers (or polymorphisms) that may be studied that relate to the etiology of PsA include HLA C\*0602 alleles. Polymorphisms in genes that relate to the mechanism of action may include the nonsynonymous polymorphisms in IL17A (S141S, R134R), IL17A receptor (V367A, Q562P) and related genes.

Despite continuing advances in genetics research, not all of the polymorphisms relevant to drug metabolism, drug action and PsA have been identified. Therefore, additional polymorphisms will be added within the restricted scope of these studies as described above.

In addition, recent advances in genotyping technologies have made genome-wide association (GWA) studies possible. GWA studies may also be undertaken within the restricted scope of these studies as described above.

At all study sites, one optional blood sample will be collected in subjects for pharmacogenetics assessment at baseline (Visit 2) as indicated in [Table 6-1](#).

Lab manuals will be provided with detailed information on sample collection, handling, and shipment. The actual sample collection date must be entered on the central lab assessment eCRF.

Any DNA derived from the sample that remains after analysis may be stored for up to 15 years to address scientific questions related to secukinumab or PsA.

**Table 6-6 PG sample log**

Visit	Week	PG Sample number	mL
2	0	1301	10

### **Sample analytical methods:**

Covance Central Laboratory Services is using the Qiagen Autopure Extraction Robot for Genomic DNA Extraction from EDTA Whole Blood. Genotyping will be conducted by the Genomic and Genetic Applications (GGA) Cambridge laboratory utilizing Taqman endpoint detection sequencing or real-time PCR-based techniques.

#### **6.6.3.1 Serum biomarkers related to targeted pathway**

Biomarkers are objectively measured and evaluated indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention ([Biomarkers](#)

[Definitions Working Group 2001](#)). This search for biomarkers of disease and drug response will involve an integrated molecular approach examining genetic and serum protein profiles. These exploratory assessments aim to identify potential markers of response and/or loss of response, and to characterize molecular mechanisms of treatment with secukinumab.

Any biomarker samples may be stored for up to 20 years (depending on local regulations) to research scientific questions related to secukinumab, RA and related diseases with a potential involvement of IL-17A. The material can be destroyed on subject's request at any time point.

Details on the collections, handling and shipment of the samples to the central laboratory will be provided to investigators in the laboratory manual.

Any results from these exploratory biomarker assessments will be reported separately.

Serum biomarkers related to systemic inflammation, bone and joint metabolism and cardiovascular risk will be measured. The final selection of analytes will be driven by assay availability, new information from the public domain, results obtained in other secukinumab clinical studies, as well as by hypotheses generated by other exploratory biomarker assessments. In addition, selected markers exploring the effect of secukinumab treatment on co-morbidities may be assessed.

### **Blood collection and processing:**

At all study sites, blood samples will be collected for soluble serum markers pre-dose at the scheduled timepoints as indicated in [Table 6-1](#).

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Samples should then be processed and shipped as detailed in the laboratory manual.

The actual sample collection date will be entered on the corresponding eCRF. Sampling problems will be noted in the Comments section of the eCRF.

## **7 Safety monitoring**

### **7.1 Adverse events**

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after the subject has signed the Informed Consent Form even if the event is not considered to be related to study treatment. Medical conditions/diseases present before the subject has signed the Informed Consent Form are only considered adverse events if they worsen after the subject has signed the Informed Consent Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should 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, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study treatment(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

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

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see [Section 7.2](#).**

All adverse events should be treated appropriately. Action taken with study treatment should include one of the following: none, dose adjusted, temporarily interrupted, permanently discontinued, unknown or not applicable. Additionally, information must be provided whether a concomitant medication or non-drug therapy was given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

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

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

## 7.2 Serious adverse event reporting

To ensure subject safety, every SAE (regardless of suspected causality) occurring after the subject has signed the Informed Consent Form and until 12 weeks after last administered dose of study treatment or 30 days after the subject has stopped study participation (whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

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

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

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to study treatment, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department (DS&E). The telephone and telecopy number of the contact persons in the local department of DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an IN to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

## 7.3 Pregnancies

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis DS&E Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

## **7.4 Data monitoring and adjudication committees**

### **Data monitoring committee**

A data monitoring committee (DMC) will review the safety data of this trial at regular intervals. Details regarding the DMC process will be available in the relevant secukinumab DMC charter.

### **Adjudication committee**

An independent adjudication committee consisting of external experts may be used to monitor specific safety events, including, but potentially not limited to clinically significant cardio- and cerebro-vascular events. The events will be blindly reviewed and adjudicated as they occur during the conduct of the trial.

Details regarding the adjudication process will be available in the relevant secukinumab Adjudication Committee charter.

## **8 Data review and database management**

### **8.1 Site monitoring**

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

The investigator must maintain source documents for each 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 (e)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 (e)CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the (e)CRFs



are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

## **8.2 Data collection**

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

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

## **8.3 Database management and quality control**

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

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis .

ECG readings will be processed centrally and the results will be sent electronically to Novartis.

Subjects will use electronic pens to enter PRO data. The system will be supplied by a vendor who will also manage the database. The data will be processed centrally and the results will be transferred electronically to the Novartis database.

Randomization codes and data about all study treatment dispensed to the subject will be tracked using an IRT system. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

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

## Pharmacogenetic and exploratory biomarkers samples

To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the subject's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the subject's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

The use of pharmacogenetics to search for biomarkers of disease and drug action is exploratory. Any results from this pharmacogenetic study will not be placed in the subject's medical records.

## 9 Data analysis

Summary statistics for continuous variables include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. For binary or discrete variables the absolute number of 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 24-weeks of treatment unless otherwise specified (e.g. Major clinical response).

Efficacy and safety data for the placebo-controlled period (or the entire treatment period as appropriate) will be presented by the following 3 treatment groups. Subjects may be included in more than one treatment group for some analyses (e.g. exposure-adjusted adverse events over the entire treatment period). These treatment groups represent the regimens subjects will be eligible to be randomized to.

**Group 1: Secukinumab regimen 1:** secukinumab i.v. (10mg/kg) at BSL, Week 2 and 4 then secukinumab 75 mg s.c. starting at Week 8 every 4 weeks.

**Group 2: Secukinumab regimen 2:** secukinumab i.v. (10mg/kg) at BSL, Week 2 and 4 then secukinumab 150 mg s.c. starting at Week 8 every 4 weeks

**Group 3: Placebo regimen:** Placebo i.v. at BSL, Week 2 and 4 then placebo s.c. starting at Week 8 injected every 4 weeks

Note that the treatment groups above 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 9.1](#) 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 in case of rescue or re-randomization.

### 9.1 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 IRT) will be excluded from the randomized set.

**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 actual stratum, if stratified randomization is used.

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

## 9.2 Subject demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline 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.

Baseline comparability of the randomized treatment groups will be assessed for the following demographic variables:

- Gender, age, race, ethnicity, weight, height, and BMI

Baseline disease characteristics will also be compared for the following variables:

- TNF $\alpha$  history (naive or inadequate responder), ACR components, number of prior biologic PsA therapies, dose of methotrexate or other DMARD at randomization

To evaluate baseline comparability, categorical variables will be evaluated by a Cochran-Mantel-Haenszel test stratified by randomization stratum (TNF $\alpha$  history (naive or inadequate responder) and continuous variables will be evaluated by analysis of variance).

Note that these tests of comparability are performed for descriptive purposes only, and will not serve as a basis for determining entry of explanatory variables into the respective models. However, when these tests yield significant results they can be used as supportive information in interpreting the statistical analyses performed on the primary and secondary efficacy variables.

### 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 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.

### **9.3 Treatments (study treatment, rescue medication, other concomitant therapies, compliance)**

#### **Study treatment**

The analysis of study treatment data will be based on the safety set. The number of active and placebo injections and infusions received will be presented by treatment group and by epoch (study period). Descriptive statistics the duration of study treatment administered and the volume in milliliters administered will be presented by actual 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,  $\geq 1$  week,  $\geq 2$  weeks,  $\geq 3$  weeks,  $\geq 4$  weeks,  $\geq 8$  weeks, etc.) will be presented.

- Duration of exposure to study treatment is defined as the date of last dose of study treatment – date of first dose of study treatment plus 1 day
- Duration of observation is defined as date of last study visit – date of first dose of study treatment plus 1 day.

#### **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-baseline 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 psoriatic arthritis 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) and the total duration of exposure to rheumatoid arthritis therapies previously.

### **9.4 Analysis of the primary variable(s)**

Details of the testing strategy including primary and secondary endpoints are provided in [Section 9.5.1](#).

#### 9.4.1 Variable

The primary efficacy variable will be ACR20 response at Week 24. The analysis of the primary efficacy variable will be based on the FAS subjects who are TNF $\alpha$  inhibitor-naïve. Primarily, CRP will be used instead of ESR to calculate ACR response; ESR will only be used in the event CRP is missing.

#### 9.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypothesis for ACR20 being tested is that there is no difference in the proportion of subjects fulfilling the ACR20 criteria at Week 24 in any of the secukinumab regimens versus placebo regimen in subpopulation of subjects who are TNF $\alpha$  inhibitor-naïve.

Let  $p_j$  denote the proportion of ACR20 responders at Week 24 for treatment regimens  $j, j=0, 1, 2$ , where

- 0 corresponds to placebo regimen,
- 1 corresponds to secukinumab 75 mg s.c.,
- 2 corresponds to secukinumab 150 mg s.c.,

In statistical terms,  $H_j: p_j = p_0$ ,  $H_{A_j}: p_j \neq p_0$ , for the  $j^{\text{th}}$  secukinumab regimen, i.e.

$H_1$ : secukinumab 75 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24 in the subpopulation of subjects who are TNF $\alpha$  inhibitor naïve

$H_2$ : secukinumab 150 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24 in the subpopulation of subjects who are TNF $\alpha$  inhibitor naïve

The primary endpoint of ACR20 at Week 24 will be analyzed via logistic regression with treatment as a factor and weight as a covariate. Odds ratios will be computed for comparisons of secukinumab regimens versus placebo regimen utilizing the logistic regression model fitted.

For subjects meeting the criteria for early escape at Week 16, their ACR20 will be set to non-response at Week 24. This applies for all three treatment regimens in order to minimize bias.

#### 9.4.3 Handling of missing values/censoring/discontinuations

Missing data for ACR20 response and other binary efficacy variables (e.g. ACR50, ACR70, HAQ-DI response, etc.) will be handled based on a three tiered approach for drop-outs, complete missing data, and partial missing data.

1. Subjects who drop out of the trial for any reason will be considered non-responders from the time they drop out through the rest of the trial.
2. If a subject is missing all ACR components but has not dropped out of the trial, then response will be imputed using data from surrounding visits. If the visit before and after are both responses, the subject will be considered a responder. Otherwise, the subject will be considered a non-responder except when the last visit is missing, data from the two previous visits will be used with the same logic for determining response.

3. If a subject has partial missing data for a visit (i.e. only some of the ACR components), LOCF will be used to impute the missing components.

LOCF will be used as the primary analysis method for continuous variables (e.g. ACR components, DAS, etc.). For analyses of these parameters, if all post-baseline 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.

In general, the handling of data for subjects who meet the criteria for early escape at week 16 will be handled in the following fashion: For binary endpoints, subjects will be considered non-responders. For continuous endpoints, LOCF from the point of escape will be used to impute data for week 24. This applies for all 3 treatment regimens in order to minimize bias.

#### **9.4.4 Supportive analyses**

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

In order to determine the robustness of the logistic regression model used for the primary analysis, ACR20 response at Week 24 will also be evaluated using a non-parametric regression ([Koch et. al 1998](#)) model with the same independent variables as the logistic regression model. In addition, further logistic regression models may be conducted which explore the impact of other baseline or disease characteristics on response. Treatment by factor interactions will be explored.

The generalized estimating equation (GEE) method extending the logistic regression analysis will be performed to evaluate the treatment effect of secukinumab compared to placebo over time and to assess the impact of missing data. The exchangeable correlation matrix will be used, and treatment by time interaction will be explored.

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:

- Multiple imputation
- Observed data analysis
- Missing data as non-response

### **9.5 Analysis of secondary variables**

#### **9.5.1 Key secondary variables**

##### **Testing strategy**

The following primary and key secondary hypotheses will be included in the sequential testing strategy, and type-I-errors will be set such that a family-wise type-I-error of 5% is kept: Primary objectives (as described in [Section 9.4](#)):

H<sub>1</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24 in the subpopulation of subjects who are TNF $\alpha$  inhibitor naïve

H<sub>2</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24 in the subpopulation of subjects who are TNF $\alpha$  inhibitor naïve

Key secondary objectives:

H<sub>3</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24 in the whole study population

H<sub>4</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24 in the whole study population

H<sub>5</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to physical function (HAQ-DI) at Week 24 in the subpopulation of subjects who are TNF $\alpha$  inhibitor naïve

H<sub>6</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to physical function (HAQ-DI) at Week 24 in the subpopulation of subjects who are TNF $\alpha$  inhibitor naïve

H<sub>7</sub>: Secukinumab pooled regimen (75 mg and 150 mg s.c.) is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24 in the subpopulation of subjects who are TNF $\alpha$  inhibitor naïve

H<sub>8</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24 in the subpopulation of subjects who are TNF $\alpha$  inhibitor naïve

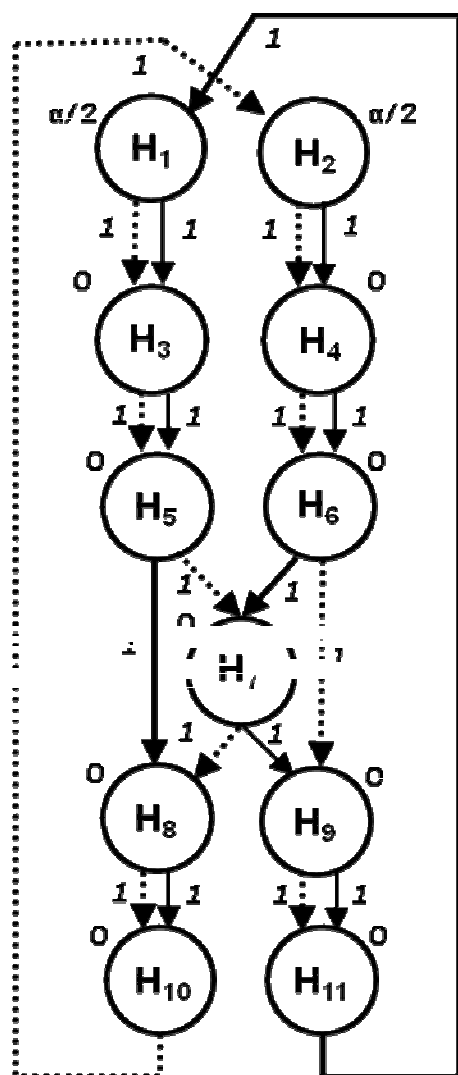
H<sub>9</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24 in the subpopulation of subjects who are TNF $\alpha$  inhibitor naïve

H<sub>10</sub>: 12 months treatment with secukinumab 75 mg s.c. is not different to delayed secukinumab treatment (i.e. approximately 6 months placebo followed by 6 months secukinumab) with respect to major clinical response (continuous six-month period of ACR70 response) at Year 1 in the subpopulation of subjects who are TNF $\alpha$  inhibitor naïve

H<sub>11</sub>: 12 months treatment with secukinumab 150 mg s.c. is not different to delayed secukinumab treatment (i.e. approximately 6 months placebo followed by 6 months secukinumab) with respect to major clinical response (continuous six-month period of ACR70 response) at Year 1 in the subpopulation of subjects who are TNF $\alpha$  inhibitor naïve

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

Figure 9-1 Testing strategy



**TNF-Naive subgroup**

Week 24 ACR20  
AIN457 vs. Placebo

**Full population: (TNF-Naive + TNF-iR**

Week 24 ACR20  
AIN457 vs. Placebo

**TNF-Naive subgroup**

Week 24 HAQ-DI  
AIN457 vs. Placebo

**TNF-Naive subgroup**

Week 24 structure endpoint  
Pooled AIN457 vs. Placebo

**TNF-Naive subgroup**

Week 24 structure endpoint  
Individual AIN457 vs. Placebo

**TNF-Naive subgroup**

Week 52 Major Clinical Response  
Individual AIN457 vs. Placebo

The family-wise error will be set to  $\alpha=5\%$  and it will be controlled with the proposed hierarchical testing strategy. With this hierarchical testing approach, each of the hypotheses ( $H_1$  and  $H_2$ ) for the primary objective (based on signs and symptoms at week 24) for each secukinumab regimen versus placebo will be tested simultaneously at  $\alpha/2$ . If at least one of  $H_1$  and/or  $H_2$  are/is rejected, then the ACR20 endpoint will be tested for the full population ( $H_3$  and/or  $H_4$ , respectively). If at least one of  $H_3$  and/or  $H_4$  is rejected, the hypothesis corresponding to physical function,  $H_5$  and/or  $H_6$ , is tested, respectively. If either of  $H_5$  or  $H_6$  is rejected, then the hypothesis corresponding to the key secondary objective on joint structure endpoint at Week 24 for testing pooled secukinumab doses versus placebo ( $H_7$ ) can be tested at  $\alpha/2$  or  $\alpha$  depending on whether one or both of  $H_5$  and  $H_6$  is rejected. If this pooled hypothesis is rejected, then hypotheses concerning individual regimens of secukinumab versus placebo can be tested for a particular regimen at  $\alpha/2$ , if the corresponding regimen's hypothesis for the primary objective and key secondary objective relating to HAQ was



rejected. Once all hypotheses within a hierarchy for a secukinumab regimen are rejected, then the respective  $\alpha/2$  can be passed on to the other regimen's hierarchy of hypotheses, if they were not already rejected at  $\alpha/2$ . Of note, in the description above, rejection of a hypothesis refers to rejection of the two-sided hypothesis; however the level of a rejected hypothesis is only passed on according to the graphical procedure for the test of another hypothesis if the treatment effect is in favor of secukinumab.

In addition to the sequential testing strategy described above, Hochberg's procedure will be used to test the primary hypotheses ( $H_1$  and  $H_2$ ) at an overall two-sided 0.125% level. This is done in order to determine whether weight of the statistical evidence in support of the primary endpoints is equivalent to that which would be required if two independent trials were conducted in this population. This additional test will be conducted in order to meet US health authority requirements.

### **ACR20 at Week 24 in the whole study population**

Response at Week 24 to ACR20 in the FAS will be evaluated using a logistic regression model with treatment and randomization stratum (TNF $\alpha$  status -naive or IR) as factors and weight as a covariate. Sensitivity analyses similar to those conducted for the TNF $\alpha$ -naive population may be conducted. The interaction between treatment and TNF $\alpha$  status (naive or IR) will be explored.

### **Physical function (HAQ-DI) at Week 24**

The change from baseline to week 24 will be the primary analysis parameter for evaluating the effect of secukinumab on physical functioning as measured by the HAQ-DI in TNF $\alpha$ -naïve subjects. Treatments will be compared by means of an ANCOVA model with treatment regimen, weight, and baseline HAQ-DI as effects. Confidence intervals for the difference between each dose of secukinumab and placebo will be calculated. Missing data will be handled using LOCF.

Sensitivity and supportive analyses for the variable will be performed as well. An analysis will also be performed with observed data, and an additional sensitivity analysis will be conducted using a non-parametric regression model (Koch 1998) with treatment regimen, weight and baseline HAQ-DI as effects. Changes from baseline in HAQ-DI values at Week 24 and other timepoints will be evaluated using a longitudinal mixed effects ANCOVA model with treatment group, , and analysis visit as factors and weight and baseline HAQ-DI as covariates. An unstructured covariance structure will be assumed for this 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 and/or secukinumab at the appropriate analysis visits.

A responder approach will also be used; the HAQ-DI change from baseline to Week 24 will be classified into response or non-response using a 0.30 improvement from baseline or not, respectively. The analysis of the binary response variable will be done via logistic regression with treatment regimen, weight, and baseline HAQ-DI as independent variables. Odds ratios will be computed for comparisons of secukinumab regimens versus placebo regimen utilizing

the logistic regression model fitted. The handling of missing data for this binary endpoint will be carried out the same way as for ACR20.

### **Joint/bone structural damage at Week 24**

The change at Week 24 from baseline van der Heijde total modified Sharp score will be evaluated using a non-parametric ANCOVA model with treatment regimen as factor and weight and baseline van der Heijde total modified Sharp score as covariates for in TNF $\alpha$ inhibitor naïve subjects. The main analysis to compare pooled secukinumab regimens (75 mgs.c. and 150 mg s.c.) and then compared to placebo followed by secukinumab regimen for the FAS TNF $\alpha$  inhibitor naïve subjects. Then each of the secukinumab regimens will be compared versus the placebo regimen via pairwise comparisons for the FAS TNF $\alpha$  inhibitor naïve subjects.

For subjects who meet the criteria for early escape at Week 16 and subjects who discontinue the study prior to Week 24, linear extrapolation will be used to impute the value at Week 24. In order to minimize bias, the extrapolation will use baseline and all post-baseline data up to the point the subject meets criteria for early escape treatment, or discontinues the study.

If baseline or all post-baseline total modified Sharp score/s is/are missing for a subject, the subject will be excluded from the analyses.

Sensitivity analyses will be performed using LOCF methodology: For subjects who meet the criteria for early escape at Week 16 and subjects who discontinue the study prior to Week 24, LOCF will be used to impute the value at Week 24.

### **Major Clinical Response at Week 52**

Major Clinical Response (MCR) at Year 1 is defined as continuous six-months of ACR70 response during the 1 year period. As the expected response rates are low, particularly in the placebo regimen, the analysis method of this binary response variable will be done using the Fisher's exact test. Secukinumab regimens will be compared to placebo followed by secukinumab regimen in a pairwise fashion with respect to the proportion of TNF $\alpha$  inhibitor naïve subjects with MCR at Year 1.

The derivation of MCR will use the ACR70 responses whose imputations for missing data done in the same fashion as the primary efficacy variable, ACR20. Of note:

- Subjects escaping early at Week 16 (including subjects meeting early escape criteria in secukinumab regimens) or discontinuing study treatment prior to Week 16 will be considered non-responders.
- Subjects who discontinue the study before week 52 will be considered non-responders
- In the 6-month period of continuous response, no more than 1 visit could be imputed.

A sensitivity analysis will also be performed with observed data. As additional sensitivity analysis, major clinical response at Year 1 will be evaluated using a logistic regression model with treatment regimen, and baseline DAS28 as effects. Odds ratios will be computed for comparisons of secukinumab regimens versus placebo regimen utilizing the logistic regression model fitted.

### **9.5.2 Efficacy variables**

The following secondary objectives will be analyzed for the FAS subjects. Summaries by each randomization strata will also be performed.

#### **Joint/bone structural damage at Week 52 and 104**

Observed joint/bone structure data at Week 52 will be compared between subjects randomized at baseline to secukinumab regimen (pooled from 2 secukinumab regimens) and placebo followed by secukinumab regimen. The change from baseline to Week 52 will be evaluated using a non-parametric ANCOVA model utilized for Week 24 and including randomization strata as a covariate.

As sensitivity analysis, for subjects with missing modified Sharp score values at Week 52, their Week 52 value will be imputed by linear extrapolation from baseline, Week 16 and Week 24, and at subject discontinuation visit (if subject discontinued prior to Week 52) to Week 52.

Summary statistics of observed data at Week 52 will be provided for each treatment regimens: secukinumab 75 mg, secukinumab 150 mg, placebo escape or switch to secukinumab 75 mg at Week 16 or 24, placebo escape or switch to secukinumab 150 mg at Week 16 or 24. Summary statistics include mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum as well as Hodges-Lehmann estimate for the median including 95% confidence interval.

Observed Joint/bone structure data at Week 104 will be summarized by treatment group. In addition, the change from week 52 will also be summarized within treatment regimen.

#### **MCR at Week 104**

Major clinical response at 104 will be summarized by treatment groups.

#### **Evidence of no disease progression at Week 24, 52 and 104**

The proportion of subjects without disease progression will be defined as those subjects who have a change in van der Heijde total modified Sharp score at Week 24 relative to baseline  $\leq 0$ . The proportion of subjects without disease progression at Week 24 will be evaluated using a logistic regression model with treatment group and randomization strata, as factors, weight and baseline van der Heijde total modified Sharp score as covariates.

If a subject discontinues from the study prior to at Week 24 or meets the criteria of early escape due to pre-defined response criteria, the subject will be classified as being a non-responder and will be classified as having experienced disease progression. If measurements are available at the two previous timepoints prior to Week 24 and the subject was classified as a responder then the subject will be classified as a responder at Week 24.

The proportion of subjects without disease progression at Week 52 and 104 will be evaluated in the same manner. At week 104, the proportion of subjects with disease progression from week 52 will also be examined.

### **PsARC and ACR20/50/70 response over time**

PsARC and ACR response at individual analysis visits will be evaluated using the logistic regression model with treatment group and randomization strata as factors and weight as a covariate. In addition, to evaluate the robustness of ACR response over time, a GEE model will be fitted that includes analysis visit and the treatment group-by-analysis visit interaction as factors. An exchangeable covariance structure will be assumed for the GEE model fitted for ACR response variable.

### **HAQ-DI over time**

Between-treatment differences in the change from baseline in HAQ-DI will be evaluated using an ANCOVA model with treatment group and randomization strata as factors, weight and baseline DAS28 score as covariates. The significance of the treatment effect 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.

HAQ-DI response over time will be evaluated in the same fashion as ACR response over time i.e. using logistic regression. Baseline HAQ-DI score and randomization strata will be used as a covariate.

### **Changes in DAS28 over time**

Between-treatment differences in the change from baseline in DAS28-CRP will be evaluated using an ANCOVA model with treatment group and randomization strata as factors, weight and baseline DAS28-CRP score as covariates. For sensitivity, a repeated measures ANCOVA will be used with treatment group, randomization strata, analysis visit, and treatment group by analysis visit interaction as factors and baseline DAS28-CRP score and weight as covariates. An unstructured covariance structure will be assumed for this model. The significance of the treatment effect 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.

### **DAS28 remission, low disease activity at Week 24 and over time**

DAS28 remission is defined as a DAS28-CRP index score less than 2.6. Low disease activity is defined as DAS28-CRP index less than or equal to 3.2. The proportion of subjects meeting these response criteria at Week 24 will be evaluated using a logistic regression model with treatment group and , randomization strata as factors, weight and baseline DAS28-CRP score as covariates.

If a subject discontinues from the study prior Week 24 or meets the criteria for early escape due to pre-defined response criteria, the subject will be classified as being a non-responder and will be classified as having not been in DAS28-CRP remission. If measurements are available at the two previous timepoints prior to Week 24 and the subject was classified as a responder then the subject will be classified as a responder at Week 24.

The Week 24 results will be confirmed by a GEE model which incorporates analysis visit and the treatment group-by-analysis visit interaction as factors and assumes an exchangeable covariance structure

### **EULAR response at Week 24 and over time**

Based on the EULAR response criteria (good responder, moderate responder, and non-responder) as determined based on the value of DAS28-CRP achieved and the magnitude of change from baseline. Between-treatment differences in EULAR response at Week 24 will be evaluated using a proportional odds regression model with treatment group and randomization strata as factor, weight and baseline DAS28-CRP score as covariates. Frequency tables will also be presented to show the response rate over time up to Week 24 and Week 52, as appropriate.

### **Changes in tender joint counts over time**

For the change in tender joint counts, since evidence from the literature would suggest that the changes from baseline are normally distributed ([van Vollenhoven 2003](#)), between-treatment differences in the change in tender joint counts will be evaluated using an ANCOVA model with treatment group and randomization strata as factors, weight and baseline tender joint counts as covariates. The significance of the secukinumab treatment effect at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

### **Change in swollen joint counts over time**

For the change in swollen joint counts, since evidence from the literature would suggest that the changes from baseline are normally distributed ([van Vollenhoven 2003](#)), Between-treatment differences in the change in swollen joint counts will be evaluated using an ANCOVA model with treatment group and randomization strata as factors, weight and baseline swollen joint counts as covariates. The significance of the secukinumab treatment effect at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

### **Change in Patient's global assessment in disease activity**

For the change in patient's global assessment, since evidence from the literature would suggest that the changes from baseline are normally distributed ([van Voellenhoven 2003](#)), between-treatment differences in the change in patient's global assessment will be evaluated using an ANCOVA model with treatment group and randomization strata as factors, weight and baseline patient's global assessment VAS score as covariates. The significance of the secukinumab treatment effect at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

### **Change in Physician's global assessment in disease activity**

For the change in physician's global assessment in disease activity, since evidence from the literature would suggest that the changes from baseline are normally distributed ([van Vollenhoven 2003](#)), between-treatment differences in the change in physician's global assessment will be evaluated using an ANCOVA model with treatment group and randomization strata as factors, weight and baseline physician's global assessment VAS score as covariates. The significance of the secukinumab treatment effect at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

### **Change in PsA Pain**

For the change in PsA pain, since evidence from the literature would suggest that the changes from baseline are normally distributed ([van Vollenhoven 2003](#)), between-treatment differences in the change in PsA pain will be evaluated using an ANCOVA model with repeated measures with treatment group and randomization strata as factors, weight and baseline pain VAS as covariates. The significance of the secukinumab treatment effect at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

### **Change in erythrocyte sedimentation rate (ESR)**

For the change in ESR, since evidence from the literature would suggest that the changes from baseline are normally distributed ([van Vollenhoven 2003](#)), between-treatment differences in the change in ESR will be evaluated using an ANCOVA model with treatment group and randomization strata, as factors, weight and baseline ESR as covariates. The significance of the secukinumab treatment effect at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

### **Change in high-sensitivity C-reactive protein (hsCRP)**

For the change in hsCRP, since evidence from the literature would suggest that the data is not normally distributed ([Huffman 2006](#)), analysis will be performed on the  $\log_e$  ratio of the treatment value vs. baseline value (calculated by dividing the post-baseline value by the baseline value and then applying the  $\log_e$  transformation) to normalize the distribution of hsCRP at each analysis visit. Between-treatment differences in the change in hsCRP relative to baseline will be evaluated using an ANCOVA model with treatment group and randomization strata, as factors and weight  $\log_e$  baseline hsCRP as covariates. The significance of the secukinumab treatment effect at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits. In addition, the 2-sided 95% confidence intervals obtained from the model will be back transformed to the original scale.

### **PASI 75 response and IGA**

PASI 75 response and IGA over time will be evaluated for those subjects in whom the assessment occurred (which is planned to be a subset of the FAS). The binary variable 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.

Missing data will be handled via LOCF.

### **mNAPSI**

The mNAPSI scores range from 0-140 for all finger and toenails. The mNAPSI score will be evaluated for those subjects in whom the assessment occurred (which is planned to be a subset of the FAS) and summarized by treatment group. Treatments will be compared using ANCOVA with treatment regimen and randomization strata as factors and baseline score and weight as covariates.

### **LDI**

LDI measures the dactylitis and the scores will be summarized by treatment group. In addition, a parametric or non-parametric ANCOVA will be used to compare the treatment groups using treatment regimen and randomization strata as factors and baseline LDI and weight as covariates.

### **LEI**

The LEI will be summarized by treatment group. In addition, a parametric or non-parametric ANCOVA will be used to compare the treatment groups using treatment regimen and randomization strata as factors and baseline LDI and weight as covariates.

## **9.5.3 Safety variables**

### **Adverse events**

Treatment emergent adverse events (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized.

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 adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event 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. Serious adverse events will also be summarized.

These summaries will be presented separately by study period.

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

Separate summaries will be provided for death, serious adverse event, other significant adverse events leading to discontinuation and adverse events 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.

For AEs of special interest (e.g. infections), time-to-event analysis will be performed, as appropriate. Results will be tabulated and the Kaplan-Meier estimates for the cumulative rate will be plotted.

When adjudication is required of major cardiovascular events (MACE), a summary of those types of events as reported by the investigator and confirmed by adjudication will be provided.

### **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 baseline and post baseline.

For each parameter, the maximum change from baseline within each study period will be evaluated analogously.

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment group. Shifts will be presented by visit as well as for most extreme values post-baseline.

### **Immunogenicity**

Summary statistics will be provided for the percent of subjects with immunogenicity. If appropriate, shift tables will also be presented.

### **Vital signs**

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

### **ECG**

Summary statistics will be presented for ECG variables by visit and treatment group. Qualitative changes will be summarized.



#### **9.5.4 Health-related Quality of Life**

The PsAQoL will be evaluated for FAS subjects where data are available. All Health-related Quality of Life will be evaluated based on FAS.

##### **EQ-5D**

The EQ-5D is a questionnaire with 5 questions (regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each with three categories (no problem, moderate problem, severe problems) and a health state assessment from 0 (worst possible health state) to 100 (best possible health state). The number and percentage of subjects in each of the three categories for each question will be presented by visit and treatment group. Chi-square tests may be used to compare treatments.

Summary statistics will be shown for the health state assessment by visit and treatment group. The change from baseline at each timepoint will be compared amongst treatments using ANCOVA

##### **SF-36**

The following variables will be evaluated:

- SF-36 domain scores.
- SF-36 domain score responders (Improvements of  $\geq 5$  points and  $\geq 10$  points will be used as measures of clinically important differences (MCIDs) in SF-36 domain scores:
  - Type I responders (improvement of  $\geq 5$  points in  $\geq 6$  domains)
  - Type II responders (improvement of  $\geq 10$  points in  $\geq 3$  domains)
- SF-36 PCS and MCS scores.
- SF-36 PCS and MCS score responders (MCIDs of  $\geq 2.5$  points and  $\geq 5$  points will be used for analysis purposes):
  - Type I responders (improvement of  $\geq 2.5$  points)
  - Type II responders (improvement of  $\geq 5$  points).

ANCOVA will be carried out to estimate treatment differences for SF-36 domain scores and SF-36 summary scores. The ANCOVA model will consider treatment group and randomization strata as factors, weight and baseline score as covariates. Contrasts will be tested at a two-sided 5% level of significance.

In the responder analyses, treatment groups will be compared with respect to response to treatment using a logistic regression model with treatment and randomization strata as factors, weight and baseline SF-36 summary score as covariates. Odds ratios with corresponding 95% confidence intervals will be estimated in addition.

## **FACIT-Fatigue**

Between-treatment differences in the change in FACIT-Fatigue total score will be evaluated using an ANCOVA model with treatment group, randomization strata as factors, weight and baseline FACIT-Fatigue total score as covariates. The significance of the treatment effect 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.

## **Dermatology Life Quality Index**

The DLQI will be evaluated for those subjects in whom the assessment occurred (which is planned to be a subset of the FAS). The DLQI measures functional disability of subjects with dermatological disorders that are greater than 18 years of age and had been utilized as a relevant clinical measure in atopic dermatitis, as well as other dermatitis clinical trials. The DLQI is a simple, validated, self-administered 10-item questionnaire. The instrument contains six functional scales (i.e., symptoms and feeling, daily activities, leisure, work and school, personal relationships, treatment). For the DLQI, each question will be answered with the following response: “not at all,” “a little,” “a lot,” or “very much”. Seven scores will be derived from the DLQI: the total score of each of the six dimensions as well as the total score over all items. The higher the score, the more quality of life is impaired.

For each of the seven scores the percentage change from baseline will be derived. Summary statistics will be provided for absolute values as well as for the percentage change by visit and treatment group.

The absolute value and the percentage change from baseline of DLQI total score will be analyzed with the Van-Elteren test using type-II weights, for all pairwise comparisons between secukinumab treatment groups versus control(s). The Van-Elteren test will be performed at each visit. Language of the questionnaire and geographical region and body weight stratum will be the strata adjusted for in the Van-Elteren test. In addition, stratified Hodges-Lehmann estimates for the median as well as confidence intervals will be derived for the absolute values and percentage change to baseline for each treatment group as well as for all pairwise comparisons between secukinumab treatment groups versus placebo.

It is understood that conclusions obtained from the confidence intervals of these estimates (mean or Hodges-Lehmann estimates for the median) will not be completely consistent with the testing results (Van-Elteren test) which constitute the key analysis for drawing conclusions.

In addition, summary statistics will be provided for number of subjects achieving DLQI 0 or 1. Secukinumab treatment groups will be compared to placebo by means of Fisher’s exact test.

## **PsAQoL**

The PsA quality of life (PsAQoL) questionnaire contains 20 individual yes/no questions where the total score is determined by the number of questions that received a “yes” response. Thus, a higher score reflects a poorer quality of life. Descriptive statistics (mean, median,

standard deviation, minimum, maximum) will be presented for each treatment group for the total score for all analysis visits including baseline and the change from baseline for all post-randomization visits. In addition, the number and percentage of subjects who responded yes and no to each questions will be presented by treatment group and analysis visit. Shift tables showing the changes in individual questions will also be presented, as appropriate between-treatment differences will be analyzed via ANCOVA.

## **WPAI-GH**

The WPAI-GH has four main outcomes and they are expressed in percentages. Descriptive statistics (mean, median, standard deviation, minimum, maximum) will be presented for each treatment group for the four outcomes including baseline and the change from baseline for all post-randomization visits will be summarized by treatment. Between-treatment differences may be analyzed via ANCOVA.

### **9.5.5 Pharmacokinetics**

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

#### **Pharmacokinetic variables**

The following pharmacokinetic parameter will be determined: C<sub>min,ss</sub>. Individual concentrations will be listed.

Biofluid concentrations will be expressed in µg/ml. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the Limit of Quantification will be treated as zero in summary statistics for concentration data only.

C<sub>min,ss</sub> will be determined using Phoenix.

During modeling of the pharmacokinetics of secukinumab, the broad principles outlined in the FDA Guidance for Industry: Population Pharmacokinetics will be followed.

#### **Statistical methods for pharmacokinetic analyses**

All completed subjects with quantifiable PK measurements of secukinumab will be included in the PK data analysis. Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. PK concentrations will be summarized by visit and treatment group. In addition to mean, standard deviation, coefficient of variation, median and quartiles, the geometric mean and geometric coefficient of variation and n(log) will be presented.

### **9.5.6 Pharmacogenetics**

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests (chi-square tests, ANCOVAs, linear and logistic regression) are used for the analyses. Additional data,

from subsequent clinical trials, are often needed to confirm associations. Alternatively, if the numbers of subjects enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

### **9.5.7 Biomarkers**

Soluble marker panel studies investigate differences in the level of expression of proteins or peptides between individuals in a given biofluid. The goal of such studies is to allow the identification of potential protein or peptide biomarkers of drug action or disease, and to better understand the associated underlying molecular mechanisms. By applying statistical analysis methods (e.g. principal component analysis) between subject groups, distinct study time points, or between study groups from other clinical trials, it may be possible to identify patterns which are associated with disease state or response to drug treatment. However, the exact type of data analysis method will depend on the type of data obtained in the study and thus the analysis of this data will be data driven.

### **9.5.8 PK/PD**

An indirect response model, driven by study treatment concentration, will be used to characterize the time course of efficacy response. Further details of the modeling approach will be specified in a modeling plan.

## **9.6 Sample size calculation**

A 5% two-sided type I error rate will be used to control for type I error. Two secukinumab doses will be tested versus placebo with respect to the primary endpoint (ACR20 response at Week 24), thus the type-I-error will be split to 2.5% two-sided for each comparison. Sample sizes will be based on this type I error assumption.

In this study population a placebo response rate of about 10% to 15% after 12 to 16 weeks were reported ([Kavanaugh 2009](#)) and ([Mease 2005](#)) for the naïve population. The response rate of 15% will be assumed for the TNF $\alpha$  inhibitor naïve population and 10% for the TNF $\alpha$  inhibitor IR-population. Based on the weighted average, the overall placebo rate is expected to be 13.5%.

The response on secukinumab is expected to be 50% in the TNF $\alpha$  inhibitor naïve population and 40% in the TNF $\alpha$  inhibitor IR-population. Based on the weighted average, the overall rate on a dose of secukinumab is expected to be 47%.

For the primary endpoint, ACR20 in the TNF $\alpha$  inhibitor naïve population, 140 subjects per group would yield approximately 99% power to detect a treatment difference of 35% (Fisher's exact test, PASS 2002).

In order to satisfy health authority requirements in the US, the same comparison will also be compared using a more stringent type I error (0.125%). Despite the smaller risk for type I error in this analysis, the study still maintains 99% power to detect the treatment difference of 35%.

## 9.7 Power for analysis of key secondary variables

Power for secondary variables was calculated using a two-sided 2.5% type I error. With an assumed placebo rate of 13.5% and secukinumab 47%, the study is over 99% powered to detect a treatment difference of ACR20 in the full FAS population, assuming 200 TNF $\alpha$  inhibitor naïve subjects per treatment arm (Fisher's exact test, PASS 2002). A standard deviation of approximately 0.5 has been observed for the change from baseline in HAQ-DI in golimumab and adalimumab trials in psoriatic arthritis. A 0.3 treatment difference is considered clinically relevant. Using those assumptions, the study has approximately over 99% power to detect a difference between secukinumab and placebo (NQuery Advisor 6.01), assuming 140 TNF $\alpha$  inhibitor naïve subjects per arm.

For structural endpoint, historical data (adalimumab) in this population showed a standard deviation of 1.2 on active drug and 2.4 on placebo at week 26. Using the standard deviations above and a clinically meaningful difference of 0.6, there is 70% power to show statistically significant differences between secukinumab (pooled 280 TNF $\alpha$  inhibitor naïve subjects) and placebo (140 TNF $\alpha$  inhibitor naïve subjects). Individual comparisons between secukinumab and placebo would have 66% power (Satterthwaite t-test, PASS 2002).

Reference data for major clinical response was not found for this population. However, it is commonly evaluated in rheumatoid arthritis. In arthritis, an active and placebo response of approximately 10% and 2% has been observed (Cimzia<sup>®</sup> (certolizumab), Orencia<sup>®</sup> (abatacept) labels). With 140 subjects per treatment arm, the study would be approximately 48% power to show a difference in this variable for TNF $\alpha$  inhibitor naïve subjects.

## 9.8 Interim Analysis

The primary efficacy analysis will be performed after all subjects have completed Week 52 assessment.

## **10 Ethical considerations**

### **10.1 Regulatory and ethical compliance**

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

### **10.2 Informed consent procedures**

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

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

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

The study includes an optional pharmacogenetic component which requires a separate signature if the subject agrees to participate. It is required as part of this protocol that the Investigator presents this option to the subject. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these pharmacogenetic assessments will in no way affect the subject's ability to participate in the main research study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or ethics committee approval will be obtained.

### **10.3 Responsibilities of the investigator and IRB/IEC**

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. 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 Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

### **10.4 Publication of study protocol and results**

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

## **11 Protocol adherence**

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the 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 it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

### **11.1 Protocol Amendments**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for subject safety may be implemented prior to IRB/IEC approval. 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 within 10 working days.

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- FDA guidance document:  
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## 13 Appendices

### 13.1 Appendix 1: Clinically notable laboratory values and vital signs

#### Safety Analyses: Expanded Limits and Notable Criteria

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.

Final Harmonization			
Laboratory Variable		Notable Criteria	
		Standard Units	SI Units
<b>LIVER FUNCTION AND RELATED VARIABLES</b>			
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
<b>RENAL FUNCTION, METABOLIC AND ELECTROLYTE VARIABLES</b>			
Creatinine (serum)		>50 % above baseline <sup>1)</sup>	>50 % above baseline <sup>1)</sup>
Potassium		<3.0 mEq/L >6.0 mEq/L	<3 mmol/L >6 mmol/L
Sodium		<115 mEq/L >160 mEq/L	<115 mmol/L >160 mmol/L

<sup>1)</sup> The baseline serum creatinine value is the pre-treatment serum creatinine level, which is defined as the creatinine level measured at screening (Visit 1).

#### HEMATOLOGY VARIABLES

Hemoglobin: 20 g/L decrease from baseline  
 Platelet count: <Lower Limit of Normal (LLN)  
 White blood cell count: <0.8 x LLN  
 Neutrophils: <0.9 x LLN  
 Eosinophils: >1.1 x ULN  
 Lymphocytes: >1.1 x ULN  
 Protein urine dipstick: ++

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

Total score: \_\_\_\_\_

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

<sup>†</sup> Current psoriasis is assigned a score of 2; all other features are assigned a score of 1

### **13.3 Appendix 3: American College of Rheumatology (ACR) Measures and Criteria of Response**

#### **Number of tender joints**

Seventy-eight joints (78) are scored as either tender or not tender: 8 distal interphalangeal, 10 proximal interphalangeal and 20 metacarpophalangeal joints of the hands, the 10 metatarsophalangeal and 10 proximal interphalangeal joints of the feet, the 2 wrists, 2 elbows, 2 shoulders, 2 acromioclavicular, 2 sternoclavicular, 2 temporomandibular, 2 hip, 2 knee, 2 talo-tibial, and 2 mid-tarsal joints.

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

#### **Number of swollen joints**

Joints are to be scored as either swollen (1) or not swollen (0). The 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<sup>©</sup>

#### **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:
  - Patient's assessment of pain,
  - Patient's global assessment of disease activity,

- Physician's global assessment of disease activity,
- Health Assessment Questionnaire (HAQ<sup>®</sup>) score,
- C-reactive protein (CRP)/Erythrocyte Sedimentation Rate (ESR).

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

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

Reference: ([Felson 1995](#))

### **13.4 Appendix 4: The Psoriatic Arthritis Response Criteria (PsARC)**

The PsARC represent a composite measure of psoriatic arthritis disease severity and include the following 4 measures:

1. Patient global assessment of disease activity (improvement of 1 on a 5-point Likert scale is required for a response)
2. Physician global assessment of disease activity (improvement of 1 on a 5-point Likert scale is required fro a response)
3. Join pain (reduction of 30% or more in total score, assessing either 68 or 78 joints, using a 4-point scale is required for a response)
4. Join swelling (reduction of 30% or more in total score, assessing either 68 or 78 joints, using a 4-point scale is required for a response)

In order to be a 'PsARC responder' patients must achieve improvement in 2 of the above mentioned 4 measures, one of which must be joint pain or swelling, without worsening in any of the 4 measures.

### 13.5 Appendix 5: Disease Activity Score (DAS)

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

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

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

#### The DAS in the clinical trials

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

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

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

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

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

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

$$\text{DAS28} = 0.56 * \text{sqrt}(\text{tender28}) + 0.28 * \text{sqrt}(\text{swollen28}) + 0.70 * \ln(\text{ESR}) + 0.014 * \text{GH}$$

The DAS28 provides you with a number on a scale from 0 to 10 indicating the current activity of the rheumatoid arthritis of your patient. A DAS28 above 5.1 means high disease activity

whereas a DAS28 below 3.2 indicates low disease activity. Remission is achieved by a DAS28 lower than 2.6 (comparable to the ARA remission criteria).

### **Disease Activity Scores using C-reactive protein**

C-reactive protein (CRP) may be used as an alternative to ESR in the calculation of the DAS or DAS28, using the formulas below. CRP is a more direct measure of inflammation than ESR, and it is more sensitive to short-term changes (Kushner 1991). CRP production is associated with radiological progression in RA (Van Leeuwen 1993), and is considered at least as valid as ESR to measure RA disease activity (Mallya 1982, Wolfe 1997). Another advantage of determination of CRP is that waiting time for the laboratory result is shorter and that in case of multicenter studies a central laboratory can be used.

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

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

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



### 13.6 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 scaling, which are each rated on a scale of 0 to 4. The scoring system for the signs of the disease (erythema, induration, and 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:

$$\text{PASI} = 0.1 (\text{Eh} + \text{Ih} + \text{Sh}) \text{Ah} + 0.3 (\text{Et} + \text{It} + \text{St}) \text{At} + 0.2 (\text{Eu} + \text{Iu} + \text{Su}) \text{Au} + 0.4 (\text{El} + \text{Il} + \text{Sl}) \text{Al}$$

where E = erythema, I = induration, S = scaling, and A = area

### PASI Scoring Worksheet

	Head	Upper extremities	Trunk	Lower extremities
1. Redness†				
2. Thickness†				
3. Scale†				
4. Sum of rows 1, 2, and 3				
5. Area score‡				
6. Score of row 4 x row 5 x the area multiplier	Row 4 x row 5 x 0.1	Row 4 x row 5 x 0.2	Row 4 x row 5 x 0.3	Row 4 x row 5 x 0.4
<b>7. Sum row 6 for each column for PASI score</b>				
a. Divide body into four areas: head, arms, trunk to groin, and legs to top of buttocks.				
b. Generate an average score for the erythema, thickness, and scale for each of the 4 areas (0=clear, 1-4=increasing severity).				
c. Sum scores of erythema, thickness, and scale for each area.				
d. Generate a percentage for skin covered with psoriasis for each area and convert that to a 0-6 scale. ‡				
e. Multiply score of item c above times item d above for each area and multiply that by 0.1, 0.2, 0.3 and 0.4 for head, arms, trunk, and legs, respectively.				
f. Add these scores to get the PASI score.				
† Erythema, thickness, and scale are measured on a 0-4 scale (none, slight, mild, moderate, severe)				
‡Area scoring criteria (score: % involvement)				
0: 0% (clear)				
1: <10%				
2: 10-<30%				
3: 30-<50%				
4: 50-<70%				
5: 70-<90%				
6: 90-100%				

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

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

#### Modified NAPSI Instructions

This tool will ask you to assess each nail abnormality for each of a subject's nails. 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 nails of a subject, consider all aspects of all of the subject's nails and place a mark on the visual analog scale giving a global assessment of their nails.

**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.

### 13.8 Appendix 8: Standard reference table for the LDI

**Table – hands (in cm)**

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

**Table – feet (in cm)**

<b>Digit</b>	<b>Men</b>	<b>Women</b>
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

## 13.9 Appendix 9: Guidelines for administering PRO questionnaires

### Before trial begin

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) and a pencil

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

Subjects should initial and date the last page of the questionnaires

Also see 'Addressing Problems and Concerns'

### After completion

Check for completeness and not for content\*

Check for multiple responses that were made in error

Data should be transcribed from the completed questionnaire to the appropriate screen on the e-CRF

File completed questionnaire in the subject study files

*\*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 this

information is as important as any of the other medical information, and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the respondent has filled in the past. If the 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 possibly the investigator. Any response which may directly impact on or reflect their medical condition (e.g. noting of severe depression) will be communicated by the coordinator to the physician.

### **The 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.

Clinical Development

Secukinumab (AIN457)

CAIN457F2306

**A randomized, double-blind, placebo-controlled,  
multicenter study of secukinumab to demonstrate the  
efficacy at 24 weeks and to assess the long term safety,  
tolerability and efficacy up to 2 years in patients with active  
psoriatic arthritis**

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## List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANA	Anti-nuclear antibodies
Anti-CCP	Anti-cyclic citrullinated peptide
AS	Ankylosing Spondylitis
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BME	Bone Marrow Edema
BMI	Body Mass Index
BSL	Baseline
CASPAR	CLASsification criteria for Psoriatic ARthritis
CFR	Code of Federal Regulations (US)
CRF	Case Report/Record Form
CRD	Clinical Research and Development
CPO	Country Pharma Organization
CRO	Contract Research Organization
CRP/hsCRP	C-reactive protein / high sensitivity C-reactive protein
CSR	Clinical Study Report
CTEP	Cancer Therapy Evaluation Program
DAS	Disease Activity Score
DMARD	Disease Modifying Antirheumatic Drug
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic acid
DS&E	Drug Safety and Epidemiology
dsDNA	Anti-double stranded DNA antibodies
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EMA/EMEA	European Medicines (Evaluation) Agency
EULAR	European League Against Rheumatism

ESR	Erythrocyte Sedimentation Rate
FACIT-Fatigue <sup>®</sup>	Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GEE	Generalized estimating equation
HAQ-DI <sup>®</sup>	Health Assessment Questionnaire – Disability Index
HIV	Human Immunodeficiency Virus
HRQoL	Health-related Quality of Life
hsCRP	High sensitivity C-Reactive Protein
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGA mod 2011	Novartis Investigator’s Global Assessment modified 2011
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	IntraUterine Device
IUS	IntraUterine System
i.v.	intravenous(ly)
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDI	Leeds Dactylitis Index
LDL	Low Density Lipoprotein
LEI	Leeds Enthesitis Index
LLN	Lower limit of normal
LOCF	Last observation carried forward
LLOQ	Lower Limit of quantification
MCR	Major Clinical Response
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities

MRD	Mean relative difference
mmHg	Millimeter mercury
MMP	Matrix Metalloprotease
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PG	Pharmacogenetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PoC	Proof of Concept
PPD	Purified protein derivative
PRN	As required
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
PsAMRIS	Psoriatic Arthritis Magnetic Resonance Imaging Scoring System
PsAQoL	Psoriatic Arthritis Quality of Life questionnaire
QoL	Quality of Life
RA	Rheumatoid Arthritis
RBC	Red Blood Cells
RF	Rheumatoid Factor
SAE	Serious adverse event
s.c.	subcutaneous(ly)
SCR	Screening
SF-36	Medical Outcome Short Form (36) Health Survey
SJC	Swollen Joint Count
SNP	Single Nucleotide Polymorphism
SpA	Spondyloarthritis
SWFI	Sterile water for injection
t.i.d.	ter in die, three times daily
TJC	Tender Joint Count
TNF	Tumor necrosis factor



TNF-IR	TNF $\alpha$ Inhibitor Incomplete Responders
ULN	Upper limit of normal
US	Unites States of America
VAS	Visual Analog Scale
WBC	White Blood Cells
WHO	World Health Organization
WPAI-GH	Work Productivity and Activity Impairment–General Health questionnaire

## Glossary of terms

Assessment	A procedure used to generate data required by the study
Control treatment	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational treatment, assess internal study validity, and/or evaluate comparative effects of the investigational treatment
Enrollment	Point/time of patient 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)
Inadequate response to TNF $\alpha$	Active disease despite stable treatment with anti-TNF $\alpha$ for at least 3 months at a stable dose or for at least one dose in the case of lack of tolerance
Investigational treatment	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new treatment."
Medication number	A unique identifier on the label of each study treatment package in studies that dispense study treatment using an IVR system
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Phase	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and assessments; at this time all study treatment administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Any treatment administered to the patient as part of the required study procedures; includes investigational treatment and any control drugs
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

## Amendment 3

### Amendment rationale

This protocol amendment is primarily issued for the following reasons:

- To expand the statistical hierarchy (primary plus ranked secondary variables) to include more endpoints which are relevant to determining the overall therapeutic value of a therapy for PsA. These endpoints include but are not limited to PASI75, PASI90, DAS28-CRP, HAQ-DI, SF-36, dactylitis and enthesitis. Psoriatic arthritis (PsA) is a multifaceted chronic disabling disease that can present as different clinical phenotypes: peripheral arthritis, axial disease, skin and nail disease, dactylitis, and enthesitis, and hence defining outcome measures has been a challenge. Traditionally endpoints for PsA studies focused only on peripheral arthritis endpoints relevant for rheumatoid arthritis. However recently there has been additional interest by Health Authorities and the scientific community in endpoints specific/more relevant for such patients (PRO e.g. SF36) and overall extra, skin related endpoints (PASI 75/90), dactylitis and enthesitis, hence these have been added in the proposed amendment hierarchy. Recent labels for Ustekinumab (Stelara), working on the same pathway as secukinumab, approved in Nov 2013 mentions skin related endpoints (PASI 90), dactylitis and enthesitis. Prior to finalizing original protocol for CAIN457F2306 there were no new approved therapies with this in the label. Thus the endpoints at that time were based on then existing knowledge. Thus it is critical that we align our analyses and endpoints with new precedence and hence the emerging demands of the field. The additional hierarchical considerations do not add any new assessments for patients; all this data is being collected already, we are only now reorganizing the hierarchy of secondary endpoints in line with new knowledge
- In addition, the analysis is changed to include all subjects in Full Analysis Set (FAS) which includes TNF $\alpha$  inhibitor naïve as well as TNF $\alpha$  inhibitor inadequate responders (TNF-IR) rather than focusing only on the subset of subjects who are TNF $\alpha$  inhibitor naïve, as the FAS would be more representative of the general population of PsA patients. There were no new therapies approved when original protocol for CAIN457F2306 was written and thus TNF $\alpha$  inhibitor naïve patients were target population in line with the then existing labels/indications. The shift from TNF $\alpha$  inhibitor naïve to FAS, to increase the generalizability of the study findings is also in keeping with the recently approved Ustekinumab label that has also been studied in mixed population of both TNF $\alpha$  inhibitor naïve as well as TNF-IR patients.
- As the primary endpoint is at Week 24 and the analysis will be carried out after all subjects have completed Week 52 visit, there is no longer a need for the sponsor to be blinded past this time point. The conduct of the interim analysis was revised in line with this. However, sites and subjects will remain blinded until all subjects complete study to ensure an unbiased assessment of the two different secukinumab doses.
- To mention only women of child bearing potential will undergo routine urine pregnancy tests (UPT). Thus this excludes postmenopausal women apart from sterile women from undergoing frequent UPT. This has been amended to avoid unnecessary UPT burden for women with confirmed menopause (defined as per section 4.2).

None of the changes made are due to safety concerns and none of the changes have an impact on the conduct of the trial or alter in any way the treatment of study subjects.

At the time of this amendment, enrollment into the study was complete with 606 subjects randomized but the data remained blinded as database lock has not occurred.

## **Changes to the protocol**

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

The wording of various sub-sections to “Study objectives” (Section 2), “Study design (Section 3.1), “Interim analysis” (section 3.5), “Treatment arms (Section 5.2), “Treatment blinding” (Section 5.4), “Efficacy” (Section 6.4), “Pregnancy and assessment of fertility” (Section 6.5.8), “Data analysis” (Section 9) and Appendix 3 and have been amended to reflect the rationale given above.

Additionally, this protocol amendment includes the correction of typographical and formatting errors and editorial changes for increased clarity of the text. Consequently, changes were implemented throughout the protocol.

None of the changes described in this amended protocol are made due to newly emerged safety considerations.

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

## **Summary of previous amendments**

### **Amendment 2 (18-Dec-2012)**

#### **Amendment rationale**

This protocol amendment is issued to update sections of the data analysis plan, specifically to update how missing values are handled. The guidance language for study treatment interruptions and discontinuation has been clarified. The notable laboratory values and guidance for subject observation post study treatment administration have been aligned with the wording used in all current secukinumab arthritis studies. None of the changes made are due to safety concerns and none of the changes have impact on the conduct of the trial or alter in any way the treatment of study subjects.

#### **Changes to the protocol**

The wording of various sub-sections to “Data analysis” (Section 9) have been amended to reflect the rationale given above.

Additionally, this protocol amendment includes the correction of typographical and formatting errors, and clarification of the wording in certain sections.

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

## **Amendment 1 (04-Aug-2011)**

### **Amendment rationale**

This protocol amendment is issued to clarify discrepancies in the protocol. However, none of the changes has an impact for the conduct of the trial or the patient's treatment.

### **Changes to the protocol**

Wording on the subject number for re-screened subject was removed. Subject will be tracked using a unique subject identifier, that will be applied within the database but not visible for the investigator and therefore the sentence was misleading.

The section 'Serum biomarkers related to targeted pathway' had been included as a subsection of 'Pharmacogenetics,' but Serum biomarkers should be a separate section This is now corrected. Furthermore, a Sample Log for serum biomarkers is now included in this section.

Additionally, we took the opportunity of this protocol amendment to correct typographical and formatting errors, and to clarify certain wordings.

## Protocol synopsis

**Title of study:** A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the safety, tolerability and long term efficacy up to 2 years in patients with active psoriatic arthritis

**Purpose and rationale:** The purpose of this 2 year study is to demonstrate efficacy on signs and symptoms of psoriatic arthritis and to assess the long term safety, tolerability and efficacy on joint/bone structure of secukinumab given as intravenous (i.v.) loading doses, followed by sub-cutaneous (s.c.) injections of two dose levels of secukinumab versus placebo in subjects with active PsA. Efficacy at Week 24 will be assessed based on signs and symptoms according to the American College of Rheumatology response criteria (ACR 20 response), whereas long term efficacy will be based on joint/bone structural preservation (X-ray) and physical function (HAQ-DI), as well as skin assessment for psoriasis signs. Treatment will continue up to 2 years to assess inhibition of joint damage and physical function.

### Objectives:

Primary objective: To demonstrate the efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo in subjects with active PsA based on the proportion of subjects achieving an ACR20 response.

Secondary objectives: To demonstrate that:

1. The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving a PASI75 response in the subgroup of subjects who have  $\geq 3\%$  skin involvement with psoriasis.
2. The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving a PASI90 response in the subgroup of subjects who have  $\geq 3\%$  skin involvement with psoriasis.
3. The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the DAS28-CRP at Week 24.
4. The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the SF36-PCS at Week 24.
5. The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the HAQ-DI at Week 24.
6. The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving an ACR50 response.
7. The improvement (change) from baseline to Week 24 on secukinumab pooled regimen (75 mg and 150 mg s.c.) is superior to placebo for joint/bone structural damage (van der Heijde modified total Sharp score).

8. The efficacy of secukinumab pooled regimen (75 mg and 150 mg s.c.) at Week 24 is superior to placebo based on the proportion of subjects with dactylitis in the subset of subjects who have dactylitis at baseline.
9. The efficacy of secukinumab pooled regimen (75 mg and 150 mg s.c.) at Week 24 is superior to placebo based on the proportion of subjects with enthesitis in the subset of subjects who have enthesitis at baseline.
10. The improvement (change) from baseline to Week 24 on secukinumab 75 or 150 mg is superior to placebo for joint/bone structural damage (van der Heijde modified total Sharp score).
11. The overall safety and tolerability of each secukinumab regimen compared to placebo as assessed by vital signs, clinical laboratory values, ECG and adverse events monitoring

**Population:** The study population will consist of a representative group of rheumatoid factor (RF) and anti-CCP negative subjects at least 18 years of age, fulfilling the CASPAR criteria and must have active psoriatic arthritis. Subjects included must report active disease despite current or previous NSAID, DMARD and/or TNF $\alpha$  inhibitor therapy.

Concomitant therapy with MTX ( $\leq 25$  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 must have signs of skin manifestations of psoriasis, defined by at least one psoriatic plaque of  $\geq 2$  cm diameter (but not in armpits, or chest between breasts, or groin) or nail changes consistent with psoriasis or documented history of plaque psoriasis.

Subjects cannot be re-screened more than once. A new Informed Consent Form must be signed for each screening

This is a multinational study and it is expected that subjects will be enrolled at approximately 150 sites. About 850 subjects will be screened for approximately 600 subjects to be randomized). A screening failure rate of 30 % and post-randomization dropout rate of 25 % is anticipated. Enrollment will stop as soon as the target number of randomized subjects is reached.

#### **Inclusion/Exclusion criteria:**

Inclusion criteria:

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

1. Male or non-pregnant, non-lactating female subjects at least 18 years of age
2. 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**  $\geq 3$  tender joints out of 78 and  $\geq 3$  swollen out of 76 (dactylitis of a digit counts as one joint each)
3. Rheumatoid factor and anti-CCP antibodies negative
4. Diagnosis of active plaque psoriasis, with at least one psoriatic plaque of  $\geq 2$  cm diameter (but not in intertriginous areas such as armpits, or chest between

breasts, or groin) or nail changes consistent with psoriasis or documented history of plaque psoriasis

Exclusion criteria:

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Chest X-ray with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician
2. Subjects who have previously been treated with more than 3 different TNF $\alpha$  inhibitors (investigational or approved)
3. Subjects taking high potency opioid analgesics (e.g., methadone, hydromorphone, or morphine)
4. Subjects who have ever received biologic immunomodulating agents except for those targeting TNF $\alpha$ , investigational or approved
5. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor
6. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)

**Investigational and reference therapy:** At baseline, eligible subjects will be randomized to one of the following three treatment arms in a ratio of 1:1:1.

- Group 1: secukinumab i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then secukinumab 75 mg s.c. starting at Week 8 and injected every 4 weeks
- Group 2: secukinumab i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks
- Group 3: Placebo i.v. at BSL, Weeks 2 and 4 then placebo s.c. starting at Weeks 8 and 12.

At Week 16 (Visit 8), all subjects will be classified as responders ( $\geq 20\%$  improvement from baseline in both tender and swollen joint counts) or non-responders and will be re-assigned/re-randomized at **Week 16** by the IRT to receive double-blind treatment up to 2 years, as follows:

- Subjects on placebo (Group 3) who are non-responders will be re-randomized to receive secukinumab 75 mg s.c. or 150 mg s.c. (1:1) every 4 weeks
- Subjects on placebo (Group 3) who are responders will continue to receive secukinumab placebo every 4 weeks until Week 24. At Week 24, these subjects will receive secukinumab 75 mg s.c. or 150 mg s.c. (1:1) every 4 weeks regardless of responder status (as dictated by the re-randomization).

**Study design:** This pivotal study uses a double-blind, randomized, parallel-group, placebo-controlled design. A screening (SCR) period running 4 weeks before randomization will be used to assess eligibility followed by a treatment period of 2 years.



At Week 24, efficacy of secukinumab treatment will be assessed based on an ACR20 response.

Subjects who complete the 2 year study may be eligible to enter a planned extension trial.

**Efficacy assessments:**

- ACR 20, 50, 70
- PsARC response
- Disease Activity Score-CRP(DAS28-CRP) and EULAR response criteria
- HAQ-DI
- Progression of structural damage by X-ray – van der Heijde total modified Sharp score and subscores
- Leeds Enthesitis Index (LEI)
- Leeds Dactylitis Index (LDI) and dactylitis count
- Psoriasis Area and Severity Index (PASI)
- Investigator's Global Assessment (mod 2011) for overall psoriatic disease
- Target lesion assessment
- Modified Nail Psoriasis Severity Index (mNAPSI)
- MRI on hands (incl. wrist) (at selected centers and in TNF $\alpha$  inhibitor naïve subjects with a swollen wrist)
- Quality of Life, fatigue, utilities and work productivity (SF-36 v2 Acute Form, FACIT-Fatigue, DLQI, PsAQoL, EQ-5D, WPAI-GH)

**Other assessments:**

- Safety and tolerability: Evaluation of all AEs and SAEs including injection site reactions, vital signs, ECGs and laboratory assessments
- Anti-secukinumab antibodies
- Smoking history
- Pharmacokinetics
- Soluble plasma protein markers related to targeted pathway and cardiovascular risk markers
- Exploratory: pharmacogenetics
- ANA, anti-dsDNA antibodies, anti-CCP antibodies,

**Data analysis:**

The primary endpoint in the study is ACR20 at Week 24 for all subjects. Secondary objectives will be to compare secukinumab to placebo according to a sequential testing procedure and include PASI75 response, PASI90 response, change from baseline in DAS28-CRP, change from baseline in SF-36-PCS, ACR50 response, change from baseline in van der Heijde modified total Sharp score, presence of dactylitis and enthesitis. Safety analyses will include summaries of adverse events, laboratory measurements, ECGs and vital signs.

## 1 Introduction

### 1.1 Background

Psoriatic arthritis (PsA) is an immune-mediated chronic inflammatory disease belonging to the spectrum of conditions commonly referred to as spondyloarthritis (SpA). The scientific community is split over the question whether to view these conditions together or consider them as separate entities (Nash 2005). For example, inflammatory back pain associated with psoriasis fit two classifications (1) AS 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 (Turiewicz 2007). This latter notion was recently corroborated by findings in a large-scale single nucleotide polymorphism (SNP) scan study, where IL23R variants that were previously linked to Crohn's disease and psoriasis (diseases that may both co-exist with spondyloarthritis) conferred risk to developing ankylosing spondylitis (Barrett 2008). Together, a common pathway including the IL-23/IL-17 axis may play a role in seronegative SpAs including psoriatic arthritis.

Psoriatic arthritis is a frequent 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. Recent efforts were aimed at defining more stringent classification criteria for standardized recruitment into clinical trials (Taylor 2006). 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 2004). The majority of patients will have psoriasis prior the associated arthritis occurs and will be under treatment for their skin disease. NSAIDs are used for musculoskeletal pain symptoms. Traditional disease modifying anti-rheumatic drugs (DMARDs) include methotrexate (MTX), sulfasalazine, cyclosporine, and leflunomide and are inadequate for a number of patients because these drugs only partially control established disease (Mease 2008).

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 2004, Tassiulas 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 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. In addition, current treatment options for patients with intolerance or an inadequate response to anti-TNF- $\alpha$  agents are limited.

IL-17 antagonism represents a novel therapeutic approach aimed at interference with the chronic inflammatory process by selectively targeting the predominant proinflammatory cytokine of the helper T17 cell subset. Additional effects of anti-IL17 on bone homeostasis via RANKL and IL-1, upstream of TNF $\alpha$ , can be inferred from animal studies (Koenders 2005). Assuming a potential role of TH17 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. Such effects may be additive or synergistic to anti-TNF, and thus may provide 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 a phase II study (CAIN457F2201) in Rheumatoid Arthritis (RA). IL-17A has been shown to play a pivotal direct pathogenetic role in both inflammatory and destructive joint tissue manifestations of RA and has direct effects on matrix metalloprotease (MMP) activation and stimulation of osteoclast-mediated bone resorption (Stamp 2004; Witowski 2004; Moseley 2003). Interim analysis of all 42 subjects enrolled in the PsA PoC study CAIN457A2206 who completed week 6, together with preliminary data from the later time points up to week 16, 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. 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. Furthermore, In a completed proof of concept study (CAIN457A2102), the effects of secukinumab administered at 3 mg/kg as a single intravenous infusion were compared with that of placebo in thirty-six subjects with active chronic plaque-type psoriasis. The study demonstrated efficacy at the 4- week endpoint and continuous efficacy at 12 weeks based on Psoriasis Area and Severity Index (PASI) and Investigator's Global Assessment mod 2009 (IGA mod 2011) endpoints.

To date, over 2,000 subjects with a variety of diseases and healthy volunteers have been enrolled into completed and ongoing studies with secukinumab, and over 1,400 subjects have been newly exposed to secukinumab at single and multiple doses ranging from 0.3 mg/kg to 10 mg/kg intravenous (i.v.) and 25 mg to 300 mg subcutaneous (s.c.). Of these, over 300 subjects have been continued on secukinumab through enrollment into extension trials. In total, 333 RA and 61 PsA subjects have been enrolled into trials with secukinumab. Full safety results including all reported adverse events are currently available for eight studies (across autoimmune indications) that have been completed. These show comparable numbers of adverse events in subjects treated with secukinumab compared to placebo without indication of any specific organ toxicity. Please refer to the Investigator Brochure for a more detailed review of the pre-clinical and clinical information on secukinumab.

## 1.2 Purpose

The purpose of this study is to demonstrate at Week 24 the efficacy and assess the safety of secukinumab given as intravenous (i.v.) loading doses, followed by sub-cutaneous (s.c.) injections of 2 dose levels of secukinumab versus placebo in subjects with active PsA. At Week 24, efficacy will be assessed based on improvement in signs and symptoms according to the American College of Rheumatology response criteria (ACR20 response), whereas long term efficacy up to 2 years will be based on joint/bone structure preservation (X-ray) and improvement in physical function (HAQ-DI), as well as skin and nail improvement for psoriasis signs.

Data from this study are aimed at supporting a global submission of the psoriatic arthritis indication.

## **2 Study objectives**

### **2.1 Primary objectives**

To demonstrate the efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo in subjects with active PsA based on the proportion of subjects achieving an ACR20 response.

### **2.2 Secondary objectives**

The secondary objectives of the study are to demonstrate:

1. The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving a PASI75 response in the subgroup of subjects who have  $\geq 3\%$  skin involvement with psoriasis.
2. The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving a PASI90 response in the subgroup of subjects who have  $\geq 3\%$  skin involvement with psoriasis.
3. The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the DAS28-CRP at Week 24.
4. The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the SF36-PCS at Week 24.
5. The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the HAQ-DI at Week 24.
6. The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving an ACR50 response.
7. The improvement (change) from baseline to Week 24 on secukinumab pooled regimen (75 mg and 150 mg s.c.) is superior to placebo for joint/bone structural damage (van der Heijde modified total Sharp score).
8. The efficacy of secukinumab pooled regimen (75 mg and 150 mg s.c.) at Week 24 is superior to placebo based on the proportion of subjects with dactylitis in the subset of subjects who have dactylitis at baseline.
9. The efficacy of secukinumab pooled regimen (75 mg and 150 mg s.c.) at Week 24 is superior to placebo based on the proportion of subjects with enthesitis in the subset of subjects who have enthesitis at baseline.
10. The improvement (change) from baseline to Week 24 on secukinumab 75 or 150 mg is superior to placebo for joint/bone structural damage (van der Heijde modified total Sharp score).
11. The overall safety and tolerability of each secukinumab regimen compared to placebo as assessed by vital signs, clinical laboratory values, ECG and adverse events monitoring

### **2.3 Exploratory Objectives**

To evaluate the efficacy of secukinumab at week 24 and other time points in subjects with active PsA, as applicable, on:

1. Structural progression as measured by the erosion and joint space narrowing (van der Heijde modified Sharp sub scores), proportion of subjects with no structural progression, and maintenance of effect over time
2. ACR20, ACR50, ACR70, PASI75, PASI90, PsARC response criteria, EULAR reponse criteria, low disease activity (DAS28  $\leq$ 3.2), disease remission (DAS28 <2.6), Major Clinical Response (MCR; any continuous six-month period of ACR70 response), and HAQ-DI response.
3. Change from baseline over time in DAS28-CRP, SF36-PCS, SF36-MCS, HAQ-DI score, ACR components, IGA mod 2011, Dactylitis count, LDI, LEI, mNAPSI, WPAI-GH, FACIT-Fatigue, PsAQoL, DLQI, EQ-5D-3L up to 2 years.
4. Proportion of subjects achieving Minimal Disease Activity ( 5 of the following 7 criteria:  $\leq$ 1 tender joint,  $\leq$ 1 swollen joint, PASI  $\leq$ 1 or IGA mod 2011  $\leq$ 1, patient assessment of pain (VAS)  $\leq$ 15, patient global assessment of disease (VAS)  $\leq$ 20, HAQ-DI  $\leq$ 0.5, tender enthesal points  $\leq$ 1).

In addition, the following will be explored:

5. The development of immunogenicity against secukinumab
6. The Pharmacokinetic/Pharmacodynamic (PK/PD) relationship of secukinumab.
7. Pharmacogenetic assessments to examine whether individual genetic variation in genes relating to drug metabolism, PsA and the drug target pathway confer differential response to secukinumab
8. Identification of potential biomarkers associated with treatment response to secukinumab or possibly correlating with the severity or progression of PsA, and impact of secukinumab on cardiovascular surrogate biomarkers.
9. To measure the effect of secukinumab on joint/bone structure preservation using MRI measurements (modified RAMRIS and JSN score).

### **3 Investigational plan**

#### **3.1 Study design**

This pivotal phase III study uses a double-blind, randomized, parallel-group, placebo controlled design. A screening period running up to 4 weeks before randomization will be used to assess eligibility followed by a treatment period of two years. At baseline (BSL), subject whose eligibility is confirmed will be randomized to one of three treatment groups:

- Group 1: Secukinumab i.v. (10mg/kg) at BSL, Weeks 2 and 4, then secukinumab 75 mg s.c. starting at Week 8 and injected every 4 weeks
- Group 2: Secukinumab i.v. (10mg/kg) at BSL, Weeks 2 and 4, then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks
- Group 3: Placebo i.v. at BSL, Weeks 2 and 4, then placebo s.c. starting at Week 8 and Week 12.

The subjects will be stratified according to being either TNF $\alpha$  inhibitor incomplete responders (IR) or TNF $\alpha$  inhibitor naïve subjects. 30% of subjects are planned to be TNF $\alpha$  inhibitor inadequate responders to ensure a representative subject population for the assessment of

efficacy and safety. Thus, it is planned to randomize approximately 180 TNF $\alpha$  inhibitor IR subjects and 420 TNF $\alpha$  inhibitor naïve subjects.

**At Week 16 (Visit 8)**, all subjects will be classified as responders ( $\geq 20\%$  improvement from baseline in both tender and swollen joint counts) or non-responders. Subjects who were randomized to placebo at baseline will be re-randomized by the Interactive Response Technology (IRT) to receive double blind treatment up to 2 years, as follows (see [Figure 3-1](#)):

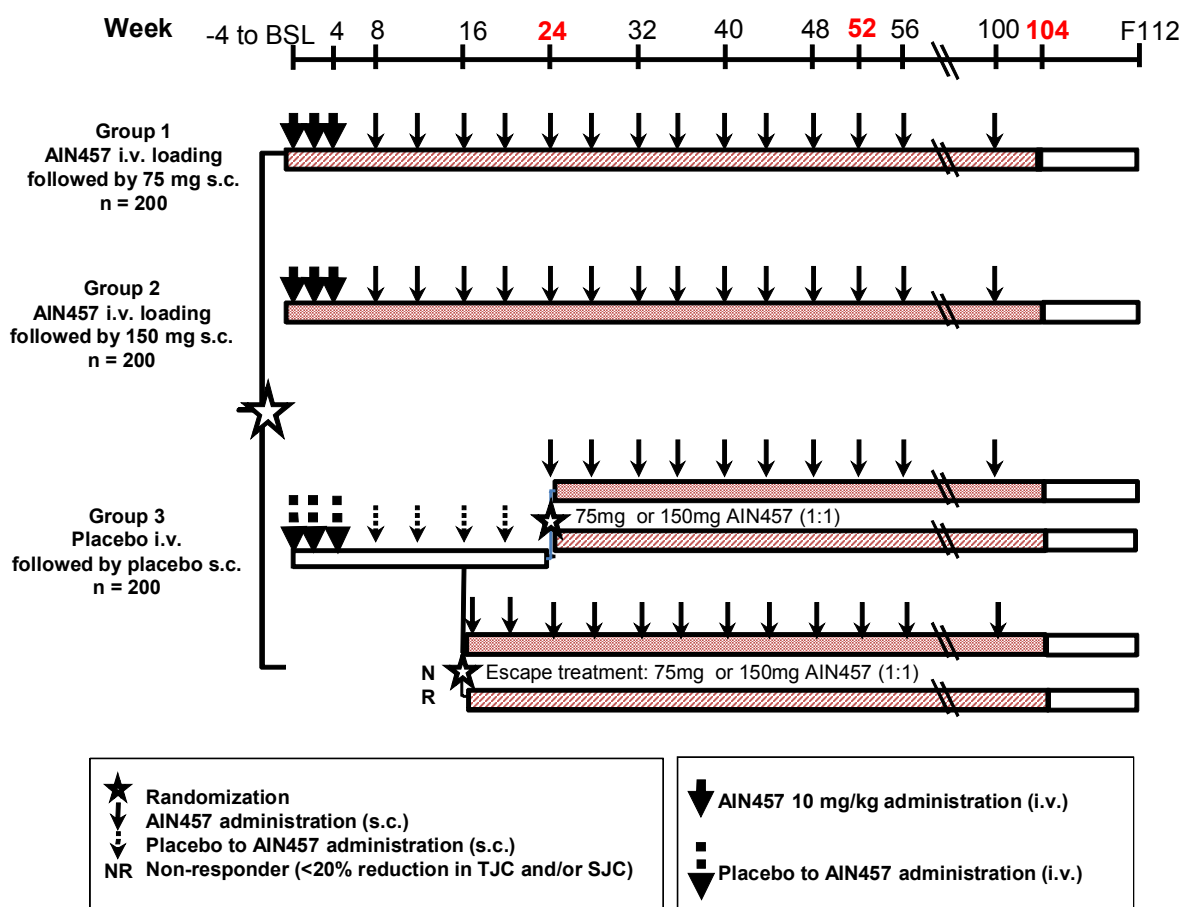
- Subjects on secukinumab placebo (Group 3) who are responders will remain on placebo until week 24. At Week 24, these subjects will receive either secukinumab 75 or 150 mg every 4 weeks (as dictated by the re-randomization).
- Subjects on secukinumab placebo (Group 3) who are non-responders will be re-randomized (1:1) at Week 16 to receive either secukinumab 75 mg or 150 mg s.c. every 4 weeks.

Rescue medication will not be allowed until Week 24. However, subjects deemed not to be benefiting from the study treatment by the investigator or for any reason on their own accord will be free to discontinue participation in the study at any time.

Subjects who complete the study may be eligible to enter a planned extension trial.

A Follow-up visit is to be done 12 weeks after last study treatment administration for subjects who early terminated the study or for subjects who completed the study but do not enter the extension study.

**Figure 3-1 Study Design**



### 3.2 Rationale of study design

The double-blind, randomized, parallel-group placebo controlled design used in this study is aligned with Phase III trials of other biologics and is in accordance with EMA guidelines (EMA 2003). The treatment duration of the placebo group is kept short and the group will be re-assigned to active treatment at the end of the primary endpoint analysis. The blinding is maintained beyond the primary endpoint so as to ensure reliable efficacy and safety measures. The regular assessments of disease activity ensures that subjects who are experiencing worsening of disease in any of the treatment groups can exit the study upon their own wish or based on the advice of the investigator at any time. Long term treatment data up to two years are being generated to demonstrate long-term efficacy and to support the safety database in this population.

### 3.3 Rationale of dose/regimen, duration of treatment

The dosing rationale for psoriatic arthritis (PsA) and ankylosing spondylitis (AS) relies upon the dose-efficacy relationship data obtained in the proof of concept (PoC) studies in Rheumatoid Arthritis (RA) (CAIN457A2101), in Ankylosing Spondylitis (AS) (CAIN457A2209) and in PsA (CAIN457A2206) along with data from the RA dose ranging trial (CAIN457F2201).

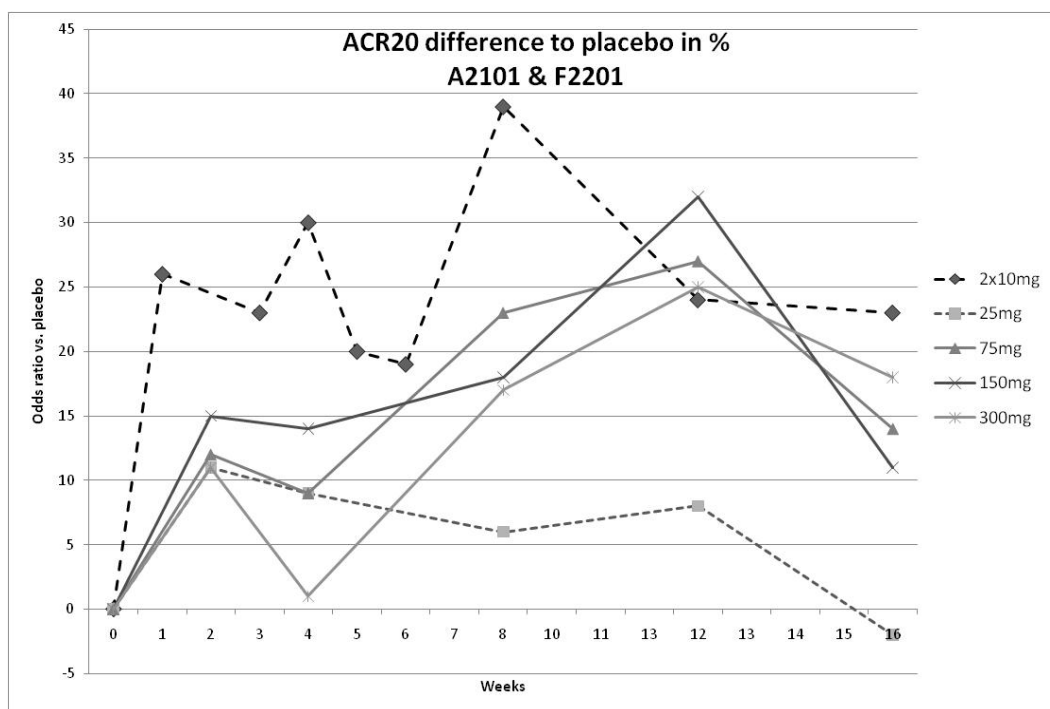
Interim analysis of all 42 subjects enrolled in study CAIN457A2206 (dosed with i.v. 2 x 10mg/kg) who completed Week 6, together with preliminary data from the later time points up to Week 16, suggest that a clinically meaningful response is induced as early as 2 weeks after start of secukinumab treatment, with further improvement up to Week 6 and maintenance of response up to Week 16.

Evidence to support a similar dose-efficacy relationship for secukinumab across the arthritides (RA, AS and PsA) is substantiated by existing evidence which indicates a degree of commonality in the pathways leading to joint damage in these chronic inflammatory diseases and a comparatively similar acute phase response and cytokine profile in the pathogenesis of the diseases. In further support of common inflammatory pathways all three conditions are responsive to both anti-IL17 and anti-TNF $\alpha$  therapy.

In the RA PoC study (CAIN457A2101), two doses of secukinumab 10 mg/kg i.v. administered at BSL and Week 3, achieved an ACR20 of 46% at Week 6 and 54% at Week 16 compared to a placebo response of 27% and 31% respectively at these time points. In contrast fixed doses of secukinumab administered at BSL and then every 4 weeks at 75, 150 and 300 mg in the RA Ph II study (CAIN457F2201) achieved an ACR20 of 48%, 40% and 39% at Week 8 and 50%, 47% and 54% at Week 16. However, placebo responses in this trial were 24% at Week 8 and 36% at Week 16. Thus the i.v. regimen employed in the PoC trial resulted in a 19% improvement in ACR20 over placebo at Week 6 and 23% at Week 16 (Figure 3-2). The fixed monthly doses of secukinumab at 75, 150 mg and 300 mg resulted in 24%, 16% and 15% improvement in ACR20 over placebo at Week 8 and 14%, 11% and 18% respectively at Week 16 (Figure 3-2). These data suggest that early high doses of secukinumab lead to increased efficacy in the first 8 weeks. Based upon these data currently planned Phase III studies in RA will be employing an i.v. loading regimen induction therapy with 10 mg/kg secukinumab administered at BSL, 2 and 4 followed by monthly secukinumab s.c. at either 75 mg or 150 mg.



**Figure 3-2 Placebo corrected ACR20 over time comparing two doses of secukinumab 10 mg/kg i.v. at BSL and 3 (CAIN457A2101) to fixed s.c. doses of secukinumab every 4 weeks (CAIN457F2201)**



To define the optimal dose for maintenance ACR, DAS28 and HAQ efficacy parameters were considered based on study CAIN457F2201. Data available from this study up to 24 weeks indicates that efficacy responses can be maintained or improved with the proposed monthly doses of 75 or 150 mg s.c.

The efficacy data from the RA study CAIN457F2201 showed that at Week 24 in the overall population as originally randomized ACR20 responses were 38 % for 25 mg, 57% for 75 mg, 58% for 150 mg and 51% for 300 mg. Non-responders in the 25 and 75 mg dose had received 1 dose of 150mg at Week 20 and non-responders in the 150 mg group had received one dose of 300 mg at Week 20. Subjects in the 300 mg cohort remained on 300 mg. Subjects switched from placebo to 150 mg after week 16 attained a 56% ACR 20 response by Week 24. These data indicate that 25 mg has similar efficacy to placebo and that 75 mg and 150 mg provided the best efficacy.

Both 75 mg and 150 mg s.c. dosed every 4 weeks in maintenance are proposed based on the totality of the data from CAIN457F2201 for phase III for the following reasons:

- 1) To ensure optimal assessment of efficacy potential for ACR responses using 2 effective s.c. doses used in phase II.
- 2) To ensure that subjects with increased inflammatory burden (i.e. high CRP) receive adequate doses of secukinumab as there is indication that they may require >75 mg.
- 3) To assess in a sufficient subject population if subjects with increased body weight require higher doses than 75 mg of secukinumab.

4) To assess the effect of secukinumab on structural benefit of the two proposed doses to see if there is a differential between these doses on this endpoint (to date no joint structure data is available for secukinumab).

5) The availability of longer term safety data for 75, 150 and 300 mg administered s.c. every 4 weeks (CAIN457F2201, CAIN457C2303).

### **3.4 Rationale for choice of comparator**

A placebo arm up to the primary endpoint at Week 24 is included in this study. Due to the nature of the disease and the outcome measures used (ACR20 criteria) a placebo arm is necessary to obtain reliable efficacy measurements. The continuation of the placebo group up to the primary endpoint at Week 24 can be supported from an ethical standpoint. Moreover the inclusion of a placebo group is in accordance with health authority guidelines, including (FDA 1999/ EMA 2003).

### **3.5 Purpose and timing of interim analyses/design adaptations**

The Week 52 analysis will be performed after all subjects have completed the Week 52 visit. For this analysis, all subjects will have completed the assessments related to the primary and key secondary objectives. Subsequent to the Week 52 analysis, the final analysis will be conducted after all subjects complete the study. 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 treatment each subject received until the end of the trial. The X-Ray and MRI interpretation will be performed by an imaging service provider and readers will be blinded to the treatment as well as visit information.

## **4 Population**

The study population will consist of a representative group of RF and anti-CCP negative subjects at least 18 years of age, fulfilling the CASPAR criteria (see [Appendix 2](#)) and must have active PsA. Subjects included must have active disease despite current or previous NSAID, DMARD and / or TNF $\alpha$  inhibitor therapy.

Concomitant therapy with MTX ( $\leq 25$  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 must have signs of skin manifestations of psoriasis, defined by at least one psoriatic plaque of  $\geq 2$  cm diameter (but not in armpits, or chest between breasts, or groin) or nail changes consistent with psoriasis or a documented history of plaque psoriasis.

This is a multinational study and it is expected that subjects will be enrolled at approximately 150 sites. About 850 subjects will be screened for approximately 600 subjects to be randomized).

A screening failure rate of 30 % and post-randomization drop-out rates of 20% at 1 year and 25% at 2 years are anticipated. Enrollment will stop as soon as the target number of randomized subjects is reached.

Subjects may only be re-screened once. A new Informed Consent Form must be signed for each screening.

#### 4.1 Inclusion criteria

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

1. Subject must be able to understand and communicate with the investigator and be able to 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 (see [Appendix 2](#)) and with symptoms for at least 6 months with moderate to severe PsA who must have **at Baseline**  $\geq 3$  tender joints out of 78 and  $\geq 3$  swollen joints out of 76 (dactylitis of a digit counts as one joint each)
4. RF and anti-CCP antibodies negative
5. Diagnosis of active plaque psoriasis, with at least one psoriatic plaque of  $\geq 2$  cm diameter (but not in intertriginous areas such as armpits, or chest between breasts, or groin) or nail changes consistent with psoriasis or a documented history of plaque psoriasis
6. Subjects with PsA should have been on NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or intolerant to NSAIDs
7. 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 24
8. Subjects taking corticosteroids must be on a stable dose of  $\leq 10$  mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 24
9. Subjects taking MTX ( $\leq 25$  mg/week) are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization and should remain on a stable dose throughout the study
10. Subjects on MTX must be on folic acid supplementation at randomization
11. Subjects who are on a DMARD other than MTX must discontinue the DMARD 28 days prior to randomization 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 $\alpha$  inhibitor must have experienced an inadequate response to previous or current treatment with a TNF $\alpha$  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 $\alpha$  inhibitor
13. Subjects who have previously been treated with TNF $\alpha$  inhibitors (investigational or approved) will be allowed entry into study after appropriate wash-out period prior to randomization:
  - a. 4 weeks for Enbrel® (etanercept) – with a terminal half-life of  $102 \pm 30$  hours (s.c. route)

- b. 8 weeks or longer for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion)
- c. 10 weeks or longer for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route)
- d. 10 weeks or longer for Simponi® (golimumab) – with a terminal half-life of 11-14 days
- e. 10 weeks or longer for Cimzia® (certolizumab) – with a terminal half-life of approx. 14 days

## 4.2 Exclusion criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Subjects taking high potency opioid analgesics (e.g., methadone, hydromorphone, or morphine)
2. Subjects who have ever received biologic immunomodulating agents except for those targeting TNF $\alpha$ , investigational or approved
3. Subjects who have previously been treated with more than 3 different TNF $\alpha$  inhibitors (investigational or approved)
4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor
5. Use of any investigational drug and/or devices within 4 weeks of randomization or 5 half-lives of the investigational drug, whichever is longer
6. 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 treatments (except in face, scalp and genital area during screening, only corticosteroids with mild to moderate potency) 2 weeks
7. Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization
8. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization
9. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 and investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
10. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for 16 weeks after stopping treatment. Effective contraception is defined as either:
  - a. Barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicides (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:

- b. 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]
- c. 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
- d. Male partner sterilization. [For female subjects on the study, the vasectomized male partner should be the sole partner for that subject]
- e. Use of established oral, injected or implanted hormonal methods of contraception, intrauterine device (IUD) or intrauterine system (IUS)

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

12. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy as judged by the investigator
13. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, infectious or gastrointestinal conditions or the management thereof which in the opinion of the investigator places the subject at unacceptable risk for participation in an immunomodulatory therapy
14. Significant medical diseases / problems, including but not limited to the following: Uncontrolled hypertension ( $\geq 160/95$  mmHg), congestive heart failure [New York Heart Association status of class III or IV], uncontrolled diabetes, or very poor functional status unable to perform self-care
15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:
  - a. Any single parameter 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 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  $\mu\text{mol/L}$ )
16. History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a creatinine level exceeding 1.5 mg/dl (132.6  $\mu\text{mol/L}$ ) at screening
17. Screening total WBC count  $< 3,000/\mu\text{l}$ , or platelets  $< 100,000/\mu\text{l}$  or neutrophils  $< 1,500/\mu\text{l}$  or hemoglobin  $< 8.5$  g/dl (85 g/L)

18. Active systemic infections during the last two weeks (exception: common cold) prior to randomization
19. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis 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  $\geq 5$  mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test as indicated in the assessment schedule (see [Table 6-1](#)). 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
20. Chest X-ray with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician
21. Known infection with HIV, hepatitis B or hepatitis C at screening or randomization
22. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that has been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant, colon polyps that have been removed)
23. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the subject unsuitable for the trial
24. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
25. Any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol
26. Donation or loss of 400 mL or more of blood within 8 weeks before dosing
27. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization
28. Plans for administration of live vaccines during the study period or 6 weeks prior randomization

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

## 5 Treatment

### 5.1 Investigational and control treatment

The appearance of the lyophilized cake for secukinumab 150 mg Powder for Solution is slightly different from secukinumab placebo to 150 mg Powder for Solution. Also, the caps for the vials of secukinumab 150 mg powder and secukinumab placebo are different colors. Therefore, in order to maintain the blind in the study, an unblinded pharmacist or unblinded qualified site personnel will be appointed at site to prepare the study treatment.

Novartis will supply the following study treatments:

- **Investigational Treatment: Secukinumab**  
Secukinumab 150 mg Powder for Solution for s.c. injection or i.v. infusion is provided in glass vials each containing 150 mg secukinumab as lyophilized cake. Secukinumab 150 mg vials are labeled as AIN457 150 mg. The vials contain a 20% overfill to allow a complete withdrawal of the labeled amount of secukinumab. The 150 mg Powder for Solution is used to prepare both the 75 mg and the 150 mg dose.
- **Reference Therapy: Secukinumab placebo (for s.c. injection):**  
Secukinumab placebo to 150 mg Powder for Solution for s.c. injection is provided in glass vials as lyophilized cake. Secukinumab placebo vials are labeled as AIN457 placebo. Each vial contains a mixture of inactive excipients, matching the composition of the secukinumab 150 mg Powder for Solution.

Reference therapy (Secukinumab placebo for i.v. infusion): 100 mL 0.9% NaCl solution is to be used as placebo for i.v. secukinumab, and is to be provided locally.

The supply will be open label.

For detailed instructions for storage, handling, reconstitution and administration of all study treatments, please refer to the pharmacist manual.

## 5.2 Treatment arms

At baseline, eligible subjects will be randomized to one of the following 3 treatment arms in a ratio of 1:1:1:

- **Group 1:** Secukinumab i.v. (10 mg/kg) at BSL, Weeks 2 and 4, then secukinumab 75 mg s.c. starting at Week 8 and injected every 4 weeks
- **Group 2:** Secukinumab i.v. (10 mg/kg) at BSL, Weeks 2 and 4, then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks
- **Group 3:** Placebo i.v. at BSL, Weeks 2 and 4, then placebo s.c. starting at Week 8 and Week 12.

**At Week 16 (Visit 8)**, all subjects will be classified as responders ( $\geq 20\%$  improvement from baseline in both tender and swollen joint counts) or non-responders. Subjects who were randomized to placebo at baseline will be re-randomized by the Interactive Response Technology (IRT) to receive double blind treatment up to two years, as follows (see [Figure 3-1](#)):

- Subjects on placebo (Group 3) who are responders will remain on placebo until week 24. At Week 24, these subjects will receive either secukinumab 75 or 150 mg every 4 weeks, regardless of responder status (as dictated by the re-randomization).
- Subjects on placebo (Group 3) who are non-responders will be re-randomized (1:1) at Week 16 to receive either secukinumab 75 mg or 150 mg s.c. every 4 weeks.

## 5.3 Treatment assignment

At baseline (Visit 2), all eligible subjects will be randomized via the Interactive Response Technology (IRT) to one of the treatment arms. The IRT can be contacted via the Interactive Voice Response System (IVRS) or interactive web response system (IWRS). The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the

inclusion criteria and does not fulfill any exclusion criterion. 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 unique medication numbers for the first packages of study treatment to be prepared for the subject. The unique medication number will be communicated to the unblinded pharmacist or unblinded qualified site personnel. The randomization number will not be communicated to any of the site staff including the unblinded pharmacist or unblinded qualified site personnel. However, the unblinded pharmacist/unblinded qualified site personnel will know what treatment the subject is receiving due to the open-label packaging of the study treatments and the fact that he/she will prepare the study treatment to be administered to the subject by the blinded site personnel.

At Visit 8 (Week 16), the IRT will also ask for the subject's responder status (responder/non-responder). The IRT will not generate the medication number of the vial(s) to be administered for Week 16 if the subject's responder status is missing. IRT will only communicate to the caller the medication numbers, not the randomization number.

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 Drug Supply Management using a validated system that automates the sequential assignment of medication numbers to study treatment packs containing each of the study treatments.

Randomization will be stratified according to being either TNF $\alpha$  IR or TNF $\alpha$  inhibitor naïve subjects. 30% of subjects should be TNF $\alpha$  inhibitor IR to ensure a representative subject population for the assessment of efficacy and safety. It is planned to randomize approximately 180 TNF $\alpha$  inhibitor IR subjects and 420 TNF $\alpha$  inhibitor naïve subjects.

The randomization scheme for subjects will be reviewed and approved by a member of the Novartis Audit Readiness, Validation and Randomization Group within IIS IA&R (Integrated Information Science Integrated Analytics and Reporting).

## 5.4 Treatment blinding

This is a double-blind, randomized treatment trial. Subjects, investigator staff (with the exception of the unblinded pharmacist), persons performing the assessments, and data analysts will remain blinded to the identity of the treatment from the time of randomization until 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, the Novartis unblinded monitors and for the preparation of the study treatment, an independent, unblinded pharmacist/nurse/physician or authorized personnel at the investigator's site who will prepare the study treatment for subjects. (2) The identity of the secukinumab/placebo treatments will be concealed by the use of study treatments in form of syringes or i.v. infusion bags filled with reconstituted secukinumab/placebo solutions that are identical in appearance, but the actual secukinumab or placebo vials with lyophilisate will be supplied "open-label."



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

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

Whenever needed or requested by the clinical team, the bioanalyst will share information from PK measurements before clinical database lock in a blinded fashion with the pharmacokineticist.

The independent, unblinded pharmacist/nurse/physician or authorized personnel will contact the IRT after randomization to receive the treatment assignment information. He/she will then prepare the study treatment. The independent, unblinded pharmacist/nurse/physician or authorized personnel will contact the IRT again at each visit between V4 and V29 to get the treatment assignment information for the subject.

The X-Ray and MRI interpretations performed by central Imaging CRO personnel will not be disclosed to investigators, site personnel, subjects and monitors during the trial.

The week 52 analysis will be performed after all subjects have completed the assessments at Week 52. Data analysts will not be blinded after Week 52 database lock. Summary results may be shared internally and externally, however individual unblinded subject data will not be disclosed. A final database lock will occur when all subjects have completed the study.

Unblinding will only occur in the case of subject emergencies (see [Section 5.5.10](#)).

## **5.5 Treating the subject**

### **5.5.1 Subject numbering**

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

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

### **5.5.2 Dispensing the study treatment**

At each visit that treatment is dispensed, an independent, unblinded pharmacist/nurse/physician or authorized personnel will identify the study treatment vials to administer to the subject by interacting with the IRT and obtaining the medication numbers

for the s.c. injection or infusion. The unblinded pharmacist/nurse/physician or authorized personnel may contact the IRT to review the treatment assignment of a subject at any time.

Immediately before preparing the treatment for administration to the subject, the unblinded pharmacist/nurse/physician or authorized personnel will document which treatment has been prepared in the source documents, Pharmacist Log, Drug Preparation Form for Unblinded Personnel, Pharmacist Drug Dispensing Form, containing that subject's unique subject number.

The study treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to a vial to be used (active or placebo). Immediately before preparation of the study treatment, the unblinded pharmacist/nurse/physician or authorized site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

### **5.5.3 Supply, storage and tracking of study treatment**

Study treatment will be supplied to each study site by Novartis as open labeled bulk medication.

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 unblinded pharmacist/nurse/physician or authorized personnel has access. Upon receipt, all study treatment should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed and administered only in accordance with the protocol.

Secukinumab lyophilisate (150 mg active/placebo) must be stored in a locked refrigerator at 2-8°C and must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

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

The unblinded pharmacist/nurse/physician or authorized personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by the unblinded field monitor during site visits and at the completion of the trial.

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

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

### **5.5.4 Instructions for prescribing and taking study treatment**

Study treatment will be administered s.c. or by i.v. infusion throughout the study by a blinded nurse/physician or blinded authorized site personnel only. Dose levels of 10 mg/kg for i.v. and either 75 mg or 150 mg s.c. of secukinumab or placebo will be administered.

Before administration to the subject, the study treatment will have to be prepared by an unblinded pharmacist/nurse or authorized site personnel appointed at the study site as outlined in the Pharmacist Manual. The unblinded pharmacist/nurse or authorized site personnel must not have any contact with the subject and must not be involved in any of the study assessments. The syringes or infusion bags with the ready-to-use study treatment solution prepared will be provided by the unblinded pharmacist/nurse or authorized personnel to the blinded investigator or assigned site staff, who will inject or infuse the subject during the study visit.

Detailed instructions on the preparation and administration of the study treatment will be described in the Pharmacist Manual and provided to each site.

Dosing should occur in the morning in order to coordinate sample collection times for PK assessments (see [Section 6.6.3](#)). Once the infusion process or the s.c. injection has been completed, and the condition of the subject is deemed stable by the investigator or designated healthcare professional, the subject can be discharged.

The first study treatment administration will occur at BSL (Visit 2) after all study scheduled assessments have been performed (and inclusion/exclusion criteria confirmed) and only after the scheduled blood samples have been drawn.

At BSL, Week 2 and Week 4 subjects will receive study treatment i.v. starting at Week 8 subjects will receive study treatment as s.c. injections every 4 weeks.

At study visits when pre-dose blood samples have to be drawn ([Table 6-1](#)), the study treatment will be injected to the subject only after the blood samples have been taken.

At Week 1 (Visit3), Week 104 (visit 30) and during the follow-up period (Visit F112), no study treatment will be administered.

All study treatments assigned to the subject during the study will be recorded in the IRT.

The subject should be instructed to contact the investigator if he/she is unable for any reason to attend the study visit as scheduled.

All dates and times of injections and infusions administered to the subject during the study must be recorded on the Dosage administration record eCRF. All injections and infusions prepared by the pharmacist should be documented in the Source Documents for Pharmacy Drug Handling.

#### **5.5.4.1 Preparation of secukinumab solution and secukinumab placebo solution for s.c. injection or infusion**

The vials containing the lyophilisate will be appropriately diluted in order to attain the correct dosage. For full details, refer to the Pharmacist Manual.

#### **5.5.4.2 Administration**

##### **For i.v. administration**

Secukinumab active/placebo should be administered i.v. using only the materials (infusion bags, infusion lines and in-line filter) specified in writing by the sponsor and as outlined in the pharmacist manual.

The entire diluted secukinumab solution in 100 mL of 0.9% NaCl solution or 100 mL of 0.9% NaCl solution for placebo doses should be administered (please see pharmacist manual for details of administration).

### **For s.c. administration**

Secukinumab active/placebo should be administered using a 27Gx0.5`` needle (1 injection of 1 mL per visit) as outlined in the pharmacist manual.

The investigator or designee should administer the study treatment by rotating body sites (thighs, arms and abdomen).

#### **5.5.4.3 After reconstitution**

From a microbiological point of view, the secukinumab Solution and secukinumab Placebo Solution for s.c. injection or for i.v. infusion, either reconstituted lyophilisate in vial, infusion bag or into the administration syringe, should be **used immediately**.

If study treatment preparation has been performed under aseptic conditions, the secukinumab Solution and secukinumab Placebo Solution for s.c. injection or for infusion might be stored at 2-8°C for no longer than 24 hours. The standing time of 24 hours is defined as the time from the first lyophilisate vial has been pierced until end of s.c. injection or infusion. If the solution is not used within the timeframe given in the Pharmacist Manual, it should be kept at 2 - 8 °C, and allowed to come to room temperature before administration (for further details, please refer to the Pharmacist Manual).

Chemical and physical in-use stability of the secukinumab Solution and secukinumab Placebo Solution for s.c. injection or infusion, either reconstituted lyophilisate in vial, infusion bag or administration syringe, has been demonstrated for up to 24 hours at 2 to 8°C.

Any unused product or waste material should be disposed of in accordance with local requirements.

#### **5.5.5 Permitted dose adjustments and interruptions of study treatment**

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

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

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

Any study treatment interruption must be recorded on the corresponding eCRF(s).

### **5.5.6 Rescue medication**

Rescue medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a subject is experiencing either no benefit from participation in the trial or worsening/exacerbation of their disease. Rescue medication must not be used before completion of Visit 10 (Week 24). Please see [Sections 5.5.7](#) and [Section 5.5.8](#) for details.

Any use of rescue medication must be recorded on the corresponding Prior and Concomitant Medications eCRF.

### **5.5.7 Concomitant treatment**

The investigator should instruct the subject to notify the study site about any new medications (including over-the-counter drugs, calcium and vitamins) he/she takes after the subject is enrolled into the study. All medications (other than study treatment) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject starts treatment with study treatment must be listed on the corresponding eCRF. The reason and the name of the drug should be listed.

Guidelines for the use of specific medications are provided below:

#### **Methotrexate**

Subjects on MTX have to be treated with stable treatment of MTX ( $\leq 25$  mg/week) for at least 4 weeks before randomization and maintained stable throughout the treatment period.

#### **Folic acid**

Subjects on MTX must be taking folic acid supplementation before randomization and during the trial to minimize the likelihood of MTX associated toxicity. Folic acid supplementation should not be taken on the same day than MTX intake.

#### **Leflunomide wash-out with cholestyramine**

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

#### **Systemic corticosteroids**

Treatment with systemic corticosteroids will be allowed if the dose was stable for at least 2 weeks before randomization and maintained stable throughout the study period. A maximum dosage of 10 mg equivalent of daily prednisone will be allowed.

Corticosteroid dose reductions are permitted after Week 24. However, for any dose reductions after Week 24, the corticosteroid dose should not be reduced more than 1 mg prednisone equivalent every 4 weeks.

Intra-articular corticosteroids are not permitted within 4 weeks prior to baseline and up to week 24. After week 24, 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 steroids is not permitted within 8 weeks prior to Weeks 24, 52, and 104.

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

**Non-steroidal anti-inflammatory drugs (NSAIDs) (COX-1 or 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 and during the treatment period.

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

However, any change of the NSAIDs, opioids, or paracetamol/acetaminophen treatment during the trial should be recorded on the corresponding eCRF.

**5.5.8 Prohibited treatment**

Use of the treatments listed in [Table 5-1](#) is NOT allowed after the start of the washout period.

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

**Table 5-1 Prohibited treatment**

<b>Prohibited treatments</b>	<b>Washout period (before randomization)</b>
Biological immunomodulating agents > 3 different TNF $\alpha$ inhibitors	Never
Etanercept	4 weeks
Infliximab	8 weeks
Adalimumab, golimumab, certolizumab	10 weeks
Unstable dose of MTX	4 weeks
Other DMARD (except MTX)	4 weeks
Leflunomide	8 weeks
Leflunomide with Cholestyramine washout	4 weeks
Unstable dose of NSAIDs (COX1 or COX2 inhibitors)	2 weeks
Systemic corticosteroids > 10 mg prednisone equivalent	2 weeks

<b>Prohibited treatments</b>	<b>Washout period (before randomization)</b>
Intra-articular steroid injections up to Week 24	4 weeks
Oral or topical retinoids	4 weeks
Photochemotherapy (e.g. PUVA)	4 weeks
Phototherapy (UVA or UVB)	2 weeks
Topical skin treatments (except in face, scalp and genital area during screening, only corticosteroids with mild to moderate potency)	2 weeks
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Analgesics other than paracetamol/acetaminophen and low strength opioids PRN	4 weeks
Live vaccinations up to Week 24	6 weeks

### 5.5.9 Discontinuation of study treatment and premature subject withdrawal

Study treatment must be discontinued and the subject withdrawn from the trial if the investigator determines that continuing it would result in a significant safety risk for that subject. The following circumstances **require** study treatment discontinuation:

- Withdrawal of informed consent
- Emergence of the following adverse events:
  - Any severe or serious adverse event that is not compatible with administration of study treatment, including adverse events that require treatment with an unacceptable co-medication up to Week 24
  - 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.
  - Life threatening infection
- Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the subject at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in Appendix 1.)
- Pregnancy
- Use of the following medication(s):
  - Any biologic immunomodulating agent except secukinumab
- Any other protocol deviation that results in a significant risk to the subject's safety

In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator.

In addition to these requirements for study treatment discontinuation, the investigator should discontinue study treatment for a given subject if, on balance, he/she thinks that continuation would be detrimental to the subject's well-being.

For subjects who discontinue study treatment a Dosage Administration Record eCRF should be completed, giving the date and primary reason for stopping study treatment. Then, all Week 104 assessments must be performed on the day of study treatment discontinuation or as early as possible after study treatment discontinuation ; and the follow up visit should be performed (F112).

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

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

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

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a subject's premature withdrawal from the study and record this information on the Study completion eCRF.

The investigator should ensure that the subject returns for an end of study visit (week 104) 4 weeks after last study treatment, and a follow-up visit (F112) 12 weeks after last study treatment. Even if the subject is not willing to come back for all assessments, every effort should be made to collect the scheduled X-ray assessments.

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

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

#### **5.5.10 Emergency unblinding of treatment assignment**

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. 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 code breaks are performed using the IRT. When the investigator contacts the system to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. The investigator will then receive details of the study 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 Clinical Trial Head that the code has been broken.

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



provide protocol number, study treatment name if available, subject number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the subject in case emergency unblinding is required at a time when the investigator and backup are unavailable.

Study treatment must be discontinued after emergency unblinding.

### **5.5.11 Study completion and post-study treatment**

A subject will be considered to have completed the study if he/she received a maximum of 100 weeks of study treatment and upon completion of all the scheduled study assessments and procedures up to and including Week 112.

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.

Study Completion evaluations must also be performed when a subject prematurely withdraws from the study for whatever reason.

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 is recommended before initiating the treatment.

### **5.5.12 Early study termination**

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the subject should be seen as soon as possible and treated as described in [Section 6](#) for 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 will be responsible for informing IRBs and/or ECs of the early termination of the trial.

## **6 Visit schedule and assessments**

[Table 6-1](#) lists all of the assessments and indicates with an "X" the visits when they are performed.

Subjects should be seen for all visits on the designated day or as closely as possible to the original planned visit schedule. For all infusion visits (Visits 2, 4 and 5), study treatment should not be administered within less than 1 week after the previous infusion. Starting at Visit 6 (Week 8), subjects should not receive study treatment within less than 2 weeks after the previous administration.

**Table 6-1 Assessment schedule**

	SCR	Treatment Period 1																Treatment Period 2										Follow-up			
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	F112 <sup>8</sup>
Week	≤4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104 <sup>13</sup> / Disc. Subj.	112
Informed consent / optional PG informed consent	X																														
Inclusion/Exclusion criteria	X	X																													
Relevant medical history/ current medical condition	X																														
Cardiovascular medical history		X																													
Psoriasis/psoriatic arthritis medical history and previous psoriasis/psoriatic arthritis therapies	X	X																													
Smoking history		X																													
Demography	X																														
Physical Exam <sup>1</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																														
Weight	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	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPD skin test <sup>2</sup> or QuantiFERON TB-Gold test	X																														
Rheumatoid factor (RF)	X																														
Anti-CCP antibodies	X									X						X														X	
Chest X-ray <sup>3</sup>	X																														
ECG (central)		X						X								X														X	
Randomization		X						X <sup>4</sup>		X <sup>4</sup>																					

	SCR	Treatment Period 1																	Treatment Period 2										Follow-up		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	F112 <sup>8</sup>
Week	≤4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104 <sup>13</sup> / Disc. Subj.	112
Administration of i.v. study treatment		X		X	X																										
Administration of s.c. study treatment						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior medication	X	X																													
Hematology, blood chemistry, local urinalysis	X	X	X	X	X	X	X	X	X	X	X	X		X			X		X		X		X		X		X		X	X	X
Serum pregnancy test	X																														
Urine pregnancy test		X			X		X	X		X		X		X			X		X		X		X		X		X		X	X	X
Con medication/non drug therapy	Update as necessary throughout the study																														
Adverse Events/SAE <sup>5</sup> (including injection site reaction & infections)	Update as necessary throughout the study																														
MRI (swollen hand/wrist; TNF-naïve subjects only) <sup>12</sup>		X					X			X																				X <sup>14</sup>	
X-Ray (hands/wrists + feet)		X						X <sup>9</sup>		X <sup>10</sup>							X													X <sup>11</sup>	
ANA		X								X							X													X	
Anti-dsDNA		X								X							X													X	
Immunogenicity		X								X							X													X	X
PK assessments (at predose)		X			X		X		X		X						X												X	X	
Tender & Swollen joint counts (TJC78 / SJC76)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		
Patient's assessment of PsA pain (VAS scale)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		
Patient's global assessment of disease activity (VAS scale)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		

	SCR	Treatment Period 1																	Treatment Period 2											Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	F112 <sup>8</sup>
Week	≤4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104 <sup>13</sup> / Disc. Subj.	112
Physician's global assessment of disease activity (VAS scale)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X			X	
Health Assessment Questionnaire (HAQ-DI)		X	X	X	X	X	X	X	X	X	X	X	X	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	X		X		X		X		X		X			X	X
Erythrocyte Sedimentation Rate (ESR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X			X	X
Leeds Dactylitis Index	X	X		X	X	X	X	X		X		X		X			X		X		X		X		X		X			X	
Leeds Enthesitis Index	X	X		X	X	X	X	X		X		X		X			X		X		X		X		X		X			X	
PASI (only if ≥ 3% of BSA at BSL)		X	X	X	X	X	X	X		X		X		X			X		X		X		X		X		X			X	
IGA (only if ≥ 3% of BSA at BSL)		X	X	X	X	X	X	X		X		X		X			X		X		X		X		X		X			X	
Target Lesion Score (TLS; only if target lesion with ≥ 2cm diameter)		X	X	X	X	X	X	X		X		X		X			X		X		X		X		X		X			X	
mNAPSI (only in subjects with nail involvement)		X	X	X	X	X	X	X		X		X		X			X		X		X		X		X		X			X	
WPAI-GH		X						X		X							X													X	
SF-36 Acute Form v2		X			X	X	X	X		X							X													X	
FACIT-Fatigue v4		X			X	X	X	X		X							X													X	
PsAQoL		X			X	X	X	X		X							X													X	
EQ-5D v3L		X			X	X	X	X		X							X													X	
DLQI (only if ≥ 3% of BSA at BSL)		X			X	X	X	X		X							X													X	
Lipids <sup>6</sup>		X				X		X		X							X							X						X	
Cardiovascular panel		X						X		X							X													X	
Serum biomarkers related to targeted pathway		X								X							X													X	

	SCR	Treatment Period 1															Treatment Period 2										Follow-up				
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	F112 <sup>8</sup>
Week	≤4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104 <sup>13</sup> / Disc. Subj.	112
Pharmacogenetics <sup>7</sup>		X																													
Treatment Period 1 Completion Form <sup>13</sup>																	X														
Treatment Period 2 Completion Form																														X	
Follow-up period Completion Form																															X

<sup>1</sup> These assessments are source documentation only and will not be entered into the eCRF

<sup>2</sup> The PPD skin test can be performed at any time during the screening period but it has to be read within 72 hrs and before randomization

<sup>3</sup> A chest X-ray is required if it was not performed and evaluated within 3 months before screening

<sup>4</sup> Subjects will be re-assigned/re-randomized to new treatment groups based on their responder status and the treatment group to which they were randomized at Visit 2

<sup>5</sup> AEs/SAEs occurring after the subject has provided informed consent must be reported

<sup>6</sup> Samples must be obtained fasting

<sup>7</sup> Pharmacogenetic sample should only be collected after separate Informed Consent Form (ICF) is signed

<sup>8</sup> Follow-up visit to be done 12 weeks after last study treatment administration for subjects who terminated the study early or for subjects who completed the study but do not enter the extension study

<sup>9</sup> X-rays only taken for subjects who are non-responder at Week 16 (only achieving < 20% reduction in both, TJC and SJC)

<sup>10</sup> X-rays only taken for subjects who are responder at Week 16 (achieving ≥ 20% reduction in both, TJC and SJC)

<sup>11</sup> Subjects who discontinue will have their X-rays taken only if more than 60 days have elapsed since their last X-rays

<sup>12</sup> Subjects who undergo the MRI assessments need to be TNFα inhibitor naïve and should have a swollen wrist at baseline; the more swollen wrist should be scanned; if both hands are equally swollen, the dominant hand should be scanned

<sup>13</sup> In case of premature discontinuation, assessments to be done 4 weeks after last study treatment administration. In case of premature discontinuation before Week 52, the Treatment Phase I Completion Form must also be completed.

<sup>14</sup> Only for subjects participating in the MRI sub-study who discontinue before or at week 24

## 6.1 Information to be collected on screening failures

Subjects may discontinue from the study prior to entering the treatment period. Those subjects 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 Screening Phase Disposition eCRF. In addition only the following eCRFs should be completed: Demography eCRF, Informed Consent eCRF, Inclusion/Exclusion eCRF, and the AE eCRF should be completed for any SAEs that occurred during the screening period.

## 6.2 Demographics/other baseline characteristics

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

- Date of birth, 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 TNF $\alpha$  inhibitor naïve or IR, cardiovascular medical history, and smoking history

Whenever possible, diagnoses and not symptoms will be recorded.

## 6.3 Treatment exposure and compliance

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

Drugs administered prior to start of treatment and other drugs continuing or started during the study treatment period will be entered in the Prior/Concomitant medications/significant non-drug therapies eCRF. Compliance is expected to be 100% (unless temporary interruption is needed for safety reasons as described in [Section 5.5.5](#)) since study treatment will be administered by the investigator or site staff. Compliance will also be assessed by a Novartis monitor using vial counts and information provided by the unblinded pharmacist/nurse/physician or authorized site personnel

## 6.4 Efficacy

- ACR 20, 50 and 70
- PsARC response
- Disease Activity Score-CRP (DAS28-CRP) and EULAR response criteria
- HAQ-DI<sup>®</sup>
- Leeds Enthesitis Index (LEI)
- Leeds Dactylitis Index (LDI) and dactylitis count
- Progression of structural damage by X-ray (hands/wrists and feet) – van der Heijde modified total Sharp score and subscores (erosion and joint space narrowing score)

- MRI of hand/wrist (in a subgroup of TNF $\alpha$  inhibitor naïve subjects at selected clinical sites only)
- Psoriasis Area and Severity Index (PASI)
- IGA (mod 2011)
- Target lesion Score
- Modified Nail Psoriasis Severity Index (mNAPSI)
- Swollen Joint Count (SJC)/Tender Joint Count (TJC)
- Patient's assessment of pain intensity (VAS scale)
- Patient's global assessment of disease activity (VAS scale)
- Physician's global assessment of disease activity (VAS scale)
- Erythrocyte Sedimentation Rate (ESR) and high sensitivity C-Reactive Protein (hsCRP)

#### **6.4.1 American College of Rheumatology (ACR) response**

The primary efficacy variable is the clinical response to treatment according to ACR20 individual improvement in disease activity at Week 24. A subject is defined as an ACR20 responder if, and only if, the following three conditions hold (See [Appendix 3](#)):

1. they have a  $\geq 20\%$  improvement in the number of tender joints (based on 78 joints)
2. they have a  $\geq 20\%$  improvement in the number of swollen joints (based on 76 joints)
3. they have a  $\geq 20\%$  improvement in three of the following five domains
  - Patient Global Assessment (measured on a VAS scale, 0-100)
  - Physician Global Assessment (measured on a VAS scale, 0-100)
  - Patient's assessment of PsA pain (measured on a VAS scale, 0-100)
  - Disability (HAQ-DI<sup>®</sup> score)
  - Acute phase reactant (hsCRP or ESR)

Additionally, Major Clinical Response (continuous six-month period of ACR70 response) will be assessed as a key secondary objective at week 52

##### **6.4.1.1 Tender 78 joint count and swollen 76 joint count**

Joint counts will be performed at scheduled visits as indicated in [Table 6-1](#), by the independent assessor(s) who must be well trained and part of the site personnel. Whenever possible, the same evaluator should perform these assessments at all visits.

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

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

#### **6.4.1.2 Patient's assessment of PsA pain intensity**

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

#### **6.4.1.3 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*".

#### **6.4.1.4 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 patient.

#### **6.4.1.5 HAQ-DI**

The HAQ-DI is a key secondary efficacy endpoint for this study. The HAQ-DI<sup>®</sup> 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.

Patient reported outcomes (PROs) will be collected using the digital pen technology. Details relating to the administration of all PROs are provided in [Appendix 9](#).

#### **6.4.1.6 High Sensitivity C-reactive protein (hsCRP)**

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



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

#### **6.4.1.7 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 (see [Table 6-1](#)).

#### **6.4.2 DAS28 and EULAR response**

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

#### **6.4.3 PsARC response**

A subject is defined as a PsARC responder if, and only if, they have an improvement in two of the following four factors (with at least one factor being a joint count) and no worsening in the remaining factors

- Patient global assessment (0-100 mm VAS scale, improvement defined as decrease of at least 20 mm)
- Physician global assessment (0-100 mm VAS scale, improvement defined as decrease of at least 20 mm)
- Tender 78-joint count (improvement defined as decrease of at least 30%)
- Swollen 76-joint count (improvement defined as decrease of at least 30%)

#### **6.4.4 Radiographic assessments**

Separate radiographs of each hand/wrist (PA) and each foot (AP) will be taken at baseline, Week 24, 52, and 104. Bone erosion, joint space narrowing (JSN), and total radiographic scores will be determined using a PsA modified van der Heijde-Sharp (vdH-S) scoring method ([van der Heijde 2005](#)) that includes the second through fifth distal interphalangeal (DIP) joints of each hand. Erosions (0–5 in the hands and 0–10 in the feet) and JSN (0–4) will be graded separately in six wrist joints, all metacarpal phalangeal, proximal interphalangeal, and DIP joints of each hand, and the first interphalangeal joint and all metatarsal phalangeal joints for each foot. The total radiographic score (hands and feet combined) ranges from 0 to 528, with higher scores indicating more articular damage. The maximum total erosion score is 360. The maximum total JSN score is 168.

The change in the Van der Heijde modified Sharp score is calculated against the baseline value. Radiologists will be trained on the X-ray acquisition and further details will be provided in a manual for the radiologists, e.g. joint placement and beam positioning.

In case of analogue X-rays films, the original film will be sent to the central reading CRO and will undergo quality control and will be digitized. Standard film and cassettes will be provided to all centers that do not produce digital X-rays. In case of digital equipment, sites

need to confirm minimum requirements with the imaging CROs Digital X-rays will be transferred electronically.

In case of insufficient quality, the center will be advised and trained on any quality issues prior to the repeat X-ray and to keep any repeat X-rays to a minimum.

Subjects who are non-responder at Week 16 (not achieving a  $\geq 20\%$  improvement from baseline in both TJC and SJC) will have their hands/wrists and feet X-rays taken at this visit (Week 16). Subjects who are responder at Week 16 ( $\geq 20\%$  improvement from baseline in both tender and swollen joint counts) will have their hands/wrists and feet X-rays taken at Week 24. Subjects who discontinue study treatment before the end of the trial, hands/wrists and feet X-rays will be taken at the time of study treatment discontinuation. However, if the radiograph performed at time of early discontinuation of study treatment is less than 60 days to a prior X-ray, it does not need to be performed. Likewise, if a scheduled X-ray at Week 24, 52, or 104 is scheduled less than 60 days after any prior hands/wrists and feet X-rays, it does not need to be performed. All following X-rays will be performed as scheduled.

The readings of the X-rays and the scoring will be performed centrally. Complete X-ray procedures will be defined in an Imaging Manual provided to the centers by an Imaging CRO designated by Novartis.

#### **6.4.5 Magnetic Resonance Imaging (MRI)**

MRI will be performed in a subgroup of approximately 90 subjects with at least one swollen wrist at baseline (approx. 30 subjects/treatment arm) at selected sites. The hand with the more swollen wrist should be chosen (determined at baseline by the investigator). If both wrists are equally affected, the dominant hand/wrist should be chosen. The site should ensure that the same hand/wrist selected at baseline will be scanned at the following visits. Subjects with any contraindications to MRI (e.g.: pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments, foreign objects in the eyes, skin or body or severe claustrophobia) or to gadolinium injections (e.g. allergic or adverse reactions to gadolinium, estimated glomerular filtration rate below 60 mL/1.73 m<sup>2</sup> (based on MRD formula)) should not perform an MRI evaluation.

MRIs will be performed at BSL, Week 12 and Week 24 using a whole body MRI system. For subjects participating in the MRI sub-study who discontinue before or at week 24, a MRI will be performed at the time of discontinuation. The MRI assessment will require gadolinium contrast agent injections. MRI machines should have a field strength of 1.5 Tesla. The MRI protocol and required sequences will be described in the imaging acquisition manual.

The readings of the scan and the scoring will be performed centrally. Readers will be blinded to clinical information and to the sequence of the images. The MRIs will be scored according to a modified OMERACT RAMRIS system ([Ostergaard 2010](#)) for erosions, bone marrow edema (BME), and synovitis. In addition, JSN will be scored ([Peterfy 2010](#)).

#### **6.4.6 Psoriasis Area and Severity Index (PASI)**

The PASI assessment will be conducted for subjects in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at baseline (Visit 2). The PASI assesses the extent of psoriasis on four body surface areas (head, trunk and upper and lower

limbs) and the degree of plaque erythema, scaling and thickness. A PASI score (Fredriksson and Pettersson 1978, Weisman 2003, Gottlieb 2005) will be derived as indicated in Table 6-2. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

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

**Table 6-2 The PASI scoring system**

Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation) (D)	Area score (based on true area %, A)*
Head (H)**	0=none	0=none	0=none	0 = 0%
	1=slight	1=slight	1=slight	1 = 1-9%
	2=moderate	2=moderate	2=moderate	2 = 10-29%
	3=severe	3=severe	3=severe	3 = 30-49%
	4=very severe	4=very severe	4=very severe	4 = 50-69%
Trunk, (T)***				5 = 70-89%
				6 = 90-100%
	0=none	0=none	0=none	0 = 0%
	1=slight	1=slight	1=slight	1 = 1-9%
	2=moderate	2=moderate	2=moderate	2 = 10-29%
	3=severe	3=severe	3=severe	3 = 30-49%
Upper limbs (U)	4=very severe	4=very severe	4=very severe	4 = 50-69%
				5 = 70-89%
				6 = 90-100%
	0=none	0=none	0=none	0 = 0%
	1=slight	1=slight	1=slight	1 = 1-9%
Lower limbs (L)****	2=moderate	2=moderate	2=moderate	2 = 10-29%
	3=severe	3=severe	3=severe	3 = 30-49%
	4=very severe	4=very severe	4=very severe	4 = 50-69%
				5 = 70-89%
				6 = 90-100%

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

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

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

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

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

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

The keys for the letters are provided in [Table 6-2](#).

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

#### 6.4.7 Investigator's Global Assessment (IGA mod 2011)

IGA mod 2011 will be conducted for overall psoriatic disease as indicated in [Table 6-3](#) for subjects in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at baseline (Visit 2). It is recommended that the same evaluator conducts the assessment throughout the study wherever possible.

The IGA mod 2011 rating scale for overall psoriatic disease is shown in [Table 6-3](#).

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

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

The IGA mod 2011 score will be recorded in the eCRF.

**Table 6-3 The IGA mod 2011 rating scale**

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

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

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

#### **6.4.8 Target lesion score (TLS)**

The Target Lesion Score will be done for subjects enrolled in the study having a psoriatic target lesion that is at least 2 cm in diameter identified at baseline (Visit 2). At the visits indicated in [Table 6-1](#), this target lesion will be scored for erythema, scaling, and thickness, each on a scale of 0 to 4 (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe). The parameter scores will be summed automatically in the eCRF, giving a score ranging from 0 to 12.

#### **6.4.9 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 ([Cassel 2007](#)). More information is provided in [Appendix 7](#).

#### **6.4.10 Leeds Dactylitis Index (LDI)**

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

#### **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.

#### **6.4.11 Leeds Enthesitis Index (LEI)**

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. Tenderness on examination is recorded as either present (1) or absent (0) for each of the 6 sites, for an overall score range of 0-6. Higher count represents greater enthesitis burden.

In this study, the lateral condyle femur L + R data were collected erroneously instead of required medial condyle femur L + R. Therefore, a 4-site LEI (LEI-4) will be calculated with the four correct sites: lateral epicondyle humerus L + R, proximal achilles L + R.

### **Presence of enthesitis**

If enthesitis is present with any of the 4 sites (lateral epicondyle humerus L + R, proximal achilles L + R), the subject is counted as a subject with enthesitis.

### **6.4.12 Appropriateness of efficacy assessments**

The efficacy outcome measures used in this study are the standard measures used across many psoriatic arthritis trials and they are required for regulatory filing.

## **6.5 Safety**

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

### **6.5.1 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 only 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.

#### **QuantiFERON TB-Gold test**

- A QuantiFERON TB-Gold test is to be performed at screening (Visit 1) 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 performed 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. 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 cleansed 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 investigators' site within that time for a proper 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  $\geq 5$  mm (or according to local practice/guidelines) is interpreted as a positive result

### **6.5.2 Physical examination**

A physical examination will be performed at scheduled visits as indicated in [Table 6-1](#). Significant findings that are present before the subject has signed the Informed Consent Form must be included in the relevant medical history eCRF. Significant findings made after the subject has signed the Informed Consent Form which meet the definition of an AE must be recorded in the Adverse Event case report form. It will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems.

### **6.5.3 Vital signs**

### **6.5.4 Height and weight**

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

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

### **6.5.5 Electrocardiogram (ECG)**

A standard 12-lead ECG will be performed at visits as indicated in [Table 6-1](#).

All ECGs must be performed on the ECG machines provided for the study.

All ECGs will be independently reviewed. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG investigator manual.

Clinically relevant abnormalities should be recorded on the relevant Medical History/Current Medical Conditions eCRF for the baseline ECG.

Clinically relevant abnormalities noted after the baseline ECG should be reported as AEs (see [Section 7](#)).

### **6.5.6 Local tolerability (injection site reactions)**

The local tolerability at the site of s.c. injection will be assessed in the case of any local reaction, until this has disappeared.

The assessment of pain, redness, swelling, induration, hemorrhage and itching will be performed by a physician and will be recorded on the Adverse Event eCRF, including the severity (none, mild, moderate, severe) and the duration.

### **6.5.7 Laboratory evaluations**

A central laboratory will be used in this study. All laboratory tests should be conducted at the central laboratory except for ESR and urinalysis/urine pregnancy tests. Central laboratory information, including collection, shipment of samples and reporting of results, may be found in the laboratory manual. For the identification of notable values, see [Appendix 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 drug related AE, is defined.

#### **6.5.7.1 Hematology**

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

#### **6.5.7.2 Clinical chemistry**

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

#### **6.5.7.3 Lipid panel**

A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), cholesterol and triglycerides will be measured from a fasting blood sample.

#### **6.5.7.4 Cardiovascular panel**

A cardiovascular profile including lipoprotein (a), apolipoprotein B, apolipoprotein A-1, and adiponectin will be measured from a blood sample.

#### **6.5.7.5 Urinalysis**

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

#### **6.5.8 Pregnancy and assessments of fertility**

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

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

#### **6.5.9 Tolerability of secukinumab**

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

#### **6.5.10 Additional parameters**

Blood will be obtained for ANA, anti-dsDNA antibodies, anti-CCP antibodies, and Rheumatoid Factor (RF) at scheduled visits as indicated in [Table 6-1](#).



### 6.5.11 Immunogenicity

Blood samples for immunogenicity (anti-secukinumab antibodies) will be taken pre-dose at the scheduled timepoints as indicated in Table 6-1. In addition, if a subject discontinues from the study at any timepoint, he/she will need to provide a sample at the last visit.

The actual sample collection date and exact time will be entered on the Immunogenicity blood collection eCRF. Sampling problems will be noted in the Comments section of the eCRF.

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

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

Tubes and preprinted labels will be provided by the central lab to the sites.

### Analytical Method

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

**Table 6-4 IG sample log**

Visit	Week	IG Sample number
2	0	301
10	24	302
17	52	303
30	104	304
F112	112	305

### 6.5.12 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic in PsA. The specific focus on infection rates in addition to the other safety measures ensures the ability to deliver data on a critical safety endpoint for this class of therapy. A Chest X-ray at screening is performed to rule out the presence of a pulmonary malignancy or infectious process, in particular tuberculosis. The radiation exposure that results from these X-ray measurements is not necessary for medical care but is intended for research purposes only. The total amount of radiation from all X-ray measurements performed in this study (1 safety chest X-ray, 3-4 X-rays of hands/wrists and feet) is estimated to be around 1 mS over 104 weeks, and is approximately equivalent to a uniform whole body exposure of 26 weeks of exposure to natural background radiation. For effective radiation doses under 3 mSv (300 mrem), the risk is considered to be "minimal". Therefore, the radiation exposure in this study

involves minimal risk and is necessary to obtain the research information desired and ensure reliable safety measures before the treatment with a biologic.

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

## 6.6 Other assessments

- Quality of Life questionnaire/ Patient reported outcomes (PROs)
- Pharmacokinetics
- Pharmacogenetics
- Serum biomarkers related to targeted pathway

### 6.6.1 Quality of Life questionnaires/Patient Reported Outcomes (PROs)

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

- HAQ-DI (see [Section 6.4.1.5](#))
- SF-36 v2 (Acute form)
- EQ-5D
- FACIT-Fatigue
- PsAQoL
- DLQI

All questionnaires will be available, where possible, in the local languages of the participating countries and should be completed by subjects before they see the study physician. The subject should be given sufficient space and time to complete the questionnaire.

Responses will be collected on digital paper to allow the use of a digital pen. Only the original digital paper provided can be used for the digital pens (i.e. these pages must not be photocopied).

All questionnaires will be completed in the respondent's local language. The study coordinator should check the questionnaires for completeness and encourage the subject to complete any missing responses. The original questionnaires will be kept with the subject's file as the source document.

Completed questionnaires should be reviewed and assessed by the investigator, before the clinical examination, for responses which may indicate potential AEs or SAEs. This assessment should be documented in the source records. If AEs or SAEs are confirmed the investigator should record the events as per instructions given in the relevant section of the protocol (see [Section 7](#)).

Guidelines for administering the PRO questionnaires can be found in [Appendix 9](#).

#### 6.6.1.1 SF-36 Version 2 (Acute Form)

The Short Form Health Survey (SF-36) is a widely used and extensively studied instrument to measure health-related quality of life among healthy subjects and patients 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 (Ware 1993). Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed (Ware 1994). 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 in this study is to assess the HRQoL of subjects. Given the acute nature of this disease, version 2, with a 1-week recall period, will be used in this study.

#### **6.6.1.2 EQ-5D**

The EQ-5D is a widely used, self-administered questionnaire designed to assess health status in adults. The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Subjects rate each of these items from "no problem," "some problem," or "extreme problem." A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is "today," and the questionnaire requires approximately 5 to 10 minutes to complete.

The EQ-5D contains six items designed to assess health status in terms of a single index value or health utility score. One of the strengths of the EQ-5D approach is that it allows "weighting" by the subject of particular health states and the generation of subject utilities. Published weights are available that allow for the creation of a single summary health utility score. Overall scores range from 0 to 1, with lower scores representing a higher level of dysfunction.

The purpose of the EQ-5D in this study is to assess the health status of subjects.

#### **6.6.1.3 FACIT-Fatigue**

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue<sup>®</sup>) is a 13-item questionnaire (Cella 1993; Yellen 1997) that assesses self-reported fatigue and its impact upon daily activities and function.

The purpose of FACIT-Fatigue<sup>®</sup> in this study is to assess the impact of fatigue on subjects with PsA.

#### **6.4.5.1. PsAQoL**

The PsAQoL is a 20-item questionnaire designed to assess the impact of PsA and its treatment on quality of life. Each item of the questionnaire is in the form of a simple statement to which subjects indicate whether or not the statement is true for them at that moment.

The theoretical basis for the PsAQoL is the needs-based model of QoL which argues that disease-related impairment and disability influences a person's ability to meet his or her needs.

#### 6.6.1.4 DLQI

The Dermatology Life Quality Index (DLQI) is a 10-item general dermatology disability index designed to assess health-related quality of life in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral warts (Finlay and Khan 1994). The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 32 different skin conditions and is available in multiple languages. The recall period is the past week, and the instrument requires 1 to 2 minutes for completion.

Each item has four response categories ranging from 0 (not at all) to 3 (very much). “Not relevant” is also a valid response and is scored as 0. The DLQI total score is a sum of the 10 questions. Scores range from 0 to 30, and higher scores indicate greater health-related quality of life impairment. Additionally, each subscale of the DLQI may be analyzed separately.

#### 6.6.1.5 Work Productivity and Activity Impairment (WPAI-GH)

The Work Productivity and Activity Impairment (WPAI-GH) questionnaire is an instrument to measure impairments in both paid work and unpaid work. It measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problem during the past seven days. The WPAI-GH consists of six questions:

- 1 = currently employed
- 2 = hours missed due to health problems
- 3 = hours missed other reasons
- 4 = hours actually worked
- 5 = degree health affected productivity while working (VAS)
- 6 = degree health affected productivity in regular unpaid activities (VAS)

The recall period for the questions 2 to 6 is seven days. Four main outcomes can be generated from the WPAI-GH and expressed in percentages.

1. percent work time missed due to health for those who were currently employed
2. percent impairment while working due to health for those who were currently employed and actually worked in the past seven days
3. percent overall work impairment due to health for those who were currently employed
4. percent activity impairment due to health for all respondents

#### 6.6.2 Pharmacokinetics

Pharmacokinetic (PK) samples will be obtained for all subjects, and secukinumab concentrations will be assessed in serum. The PK samples will be collected pre-dose at scheduled visits as indicated in [Table 6-1](#).

All blood samples will be drawn by direct venipuncture in a forearm vein.

The actual sample collection date and exact time will be entered on the PK blood collection summary eCRF. Sampling problems will be noted in the Comments section of the eCRF.

The bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the PK samples. The bioanalyst will provide the samples' concentration data to the team under blinded conditions. Both the site's unblinded pharmacist and bioanalyst will keep this information confidential until clinical database lock.

### PK sample handling, labeling and shipment instructions

Laboratory manuals will be provided by the central laboratory with detailed information on sample collection, sample handling and shipment.

Tubes and labels will be provided by the central laboratory with study/sample type information pre-printed on the label.

**Table 6-5 PK sample log**

Visit	Week	Time	Sample number	PK collection number
2	0	0 (pre-dose)	1	1
5	4	672 h (pre-dose)	2	1
8	16	2688 h (pre-dose)	3	1
10	24	4032 h (pre-dose)	4	1
17	52	8736 h (pre-dose)	5	1
30	104	17472 h (anytime)	6	1
F112	112	18816 h (anytime)	7	1

### Analytical methods

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

#### 6.6.3 Pharmacogenetics

The pharmacogenetic endpoints are exploratory and are not intended to be used for regulatory judgments pertaining to the safety or efficacy of the investigational treatment. However, these data may be considered for voluntary submission, consistent with applicable regulatory guidance on this topic, in order to develop the knowledge base necessary to establish the validity of new genomic biomarkers.

This study includes an optional exploratory pharmacogenetic assessment which requires signature of a separate informed consent if the subject agrees to participate. The identity of the subject will not be revealed. It is required as part of this protocol that the Investigator presents these options to the subject.

Exploratory pharmacogenetics studies are planned as a part of this study with the objectives of identifying inherited genetic factors that may (1) predict response to treatment with secukinumab, (2) predict relative susceptibility to drug-drug interactions, (3) predict genetic predisposition to side effects, or (4) be related to PsA and could also predict response to

treatment with secukinumab. We hope to develop a better understanding how subjects with PsA respond to secukinumab.

The genetic markers (or polymorphisms) that may be studied that relate to the etiology of PsA include HLA C\*0602 alleles. Polymorphisms in genes that relate to the mechanism of action may include the nonsynonymous polymorphisms in IL17A (S141S, R134R), IL17A receptor (V367A, Q562P) and related genes.

Despite continuing advances in genetics research, not all of the polymorphisms relevant to drug metabolism, drug action and PsA have been identified. Therefore, additional polymorphisms will be added within the restricted scope of these studies as described above.

In addition, recent advances in genotyping technologies have made genome-wide association (GWA) studies possible. GWA studies may also be undertaken within the restricted scope of these studies as described above.

At all study sites, one optional blood sample will be collected in subjects for pharmacogenetics assessment at baseline (Visit 2) as indicated in [Table 6-1](#).

Lab manuals will be provided with detailed information on sample collection, handling, and shipment. The actual sample collection date must be entered on the central lab assessment eCRF.

Any DNA derived from the sample that remains after analysis may be stored for up to 15 years to address scientific questions related to secukinumab or PsA.

**Table 6-6 PG sample log**

Visit	Week	PG Sample number	mL
2	0	1301	10

### Sample analytical methods:

Covance Central Laboratory Services is using the Qiagen Autopure Extraction Robot for Genomic DNA Extraction from EDTA Whole Blood. Genotyping will be conducted by the Genomic and Genetic Applications (GGA) Cambridge laboratory utilizing Taqman endpoint detection sequencing or real-time PCR-based techniques.

#### 6.6.4 Serum biomarkers related to targeted pathway

Biomarkers are objectively measured and evaluated indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention ([Biomarkers Definitions Working Group 2001](#)). This search for biomarkers of disease and drug response will involve an integrated molecular approach examining genetic and serum protein profiles. These exploratory assessments aim to identify potential markers of response and/or loss of response, and to characterize molecular mechanisms of treatment with secukinumab.

Any biomarker samples may be stored for up to 20 years (depending on local regulations) to research scientific questions related to secukinumab, PsA and related diseases with a potential involvement of IL-17A. The material can be destroyed on subject's request at any time point.

Details on the collections, handling and shipment of the samples to the central laboratory will be provided to investigators in the laboratory manual.

Any results from these exploratory biomarker assessments will be reported separately.

Serum biomarkers related to systemic inflammation, bone and joint metabolism and cardiovascular risk will be measured. The final selection of analytes will be driven by assay availability, new information from the public domain, results obtained in other secukinumab clinical studies, as well as by hypotheses generated by other exploratory biomarker assessments. In addition, selected markers exploring the effect of secukinumab treatment on co-morbidities may be assessed.

**Table 6-7 Serum biomarker sample log**

Visit	Week	Time	Volume (mL)	SB Sample number	SB collection number
2	0	pre-dose	2	601	1
10	24	pre-dose	2	602	1
17	52	pre-dose	2	603	1
30	104	anytime	2	604	1

### **Blood collection and processing:**

At all study sites, blood samples will be collected for soluble serum markers pre-dose at the scheduled timepoints as indicated in [Table 6-1](#).

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Samples should then be processed and shipped as detailed in the laboratory manual.

The actual sample collection date will be entered on the corresponding eCRF. Sampling problems will be noted in the Comments section of the eCRF.

## **7 Safety monitoring**

### **7.1 Adverse events**

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after the subject has signed the Informed Consent Form even if the event is not considered to be related to study treatment. Medical conditions/diseases present before the subject has signed the Informed Consent Form are only considered adverse events if they worsen after the subject has signed the Informed Consent Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should 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, laboratory test, or

other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study treatment(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

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

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see [Section 7.2](#).**

All adverse events should be treated appropriately. Action taken with study treatment should include one of the following: none, dose adjusted, temporarily interrupted, permanently discontinued, unknown or not applicable. Additionally, information must be provided whether a concomitant medication or non-drug therapy was given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

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

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



## 7.2 Serious adverse event reporting

To ensure subject safety, every SAE (regardless of suspected causality) occurring after the subject has signed the Informed Consent Form and until 12 weeks after last administered dose of study treatment or 30 days after the subject has stopped study participation (whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

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

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

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to study treatment, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department (DS&E). The telephone and telecopy number of the contact persons in the local department of DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an IN to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

## 7.3 Pregnancies

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis DS&E Department. Pregnancy follow-up should be recorded

on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

## **7.4 Data monitoring and adjudication committees**

### **Data monitoring committee**

A data monitoring committee (DMC) will review the safety data of this trial at regular intervals. Details regarding the DMC process will be available in the relevant secukinumab DMC charter.

### **Adjudication committee**

An independent adjudication committee consisting of external experts may be used to monitor specific safety events, including, but potentially not limited to clinically significant cardio- and cerebro-vascular events. The events will be blindly reviewed and adjudicated as they occur during the conduct of the trial.

Details regarding the adjudication process will be available in the relevant secukinumab Adjudication Committee charter.

## **8 Data review and database management**

### **8.1 Site monitoring**

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

The investigator must maintain source documents for each 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 (e)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 (e)CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the (e)CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

## 8.2 Data collection

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

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

## 8.3 Database management and quality control

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

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis.

ECG readings will be processed centrally and the results will be sent electronically to Novartis.

Subjects will use a digital pen to enter PRO data. The system will be supplied by a vendor who will also manage the database. The data will be processed centrally and the results will be transferred electronically to the Novartis database.

Randomization codes and data about all study treatment dispensed to the subject will be tracked using an IRT system. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

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

## Pharmacogenetic and exploratory biomarkers samples

To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the subject's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the subject's

request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

The use of pharmacogenetics to search for biomarkers of disease and drug action is exploratory. Any results from this pharmacogenetic study will not be placed in the subject's medical records.

## 9 Data analysis

Summary statistics for continuous variables include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. For binary or discrete variables the absolute number of 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 24-weeks of treatment unless otherwise specified (e.g. Major clinical response).

Efficacy and safety data for the placebo-controlled period (or the entire treatment period as appropriate) will be presented by the following 3 treatment groups. Subjects may be included in more than one treatment group for some analyses (e.g. exposure-adjusted adverse events over the entire treatment period). These treatment groups represent the regimens subjects will be eligible to be randomized to.

**Group 1: Secukinumab regimen 1:** secukinumab i.v. (10mg/kg) at BSL, Week 2 and 4 then secukinumab 75 mg s.c. starting at Week 8 every 4 weeks.

**Group 2: Secukinumab regimen 2:** secukinumab i.v. (10mg/kg) at BSL, Week 2 and 4 then secukinumab 150 mg s.c. starting at Week 8 every 4 weeks.

**Group 3: Placebo regimen:** Placebo i.v. at BSL, Week 2 and 4 then placebo s.c. starting at Week 8 every 4 weeks.

Note that the treatment groups above 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 9.1](#) 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 in case of rescue or re-randomization.

### 9.1 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 IRT) 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 actual stratum, if stratified randomization is used.

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

## 9.2 Subject demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline 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 randomized treatment groups will be summarized by the following demographic variables:

- Gender, age, race, ethnicity, weight, height, and BMI

Baseline disease characteristics will also be compared for the following variables:

- TNF $\alpha$  history (naive or inadequate responder), ACR components, number of prior biologic PsA therapies, dose of methotrexate 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.

## 9.3 Treatments (study treatment, rescue medication, other concomitant therapies, compliance)

### Study treatment

The analysis of study treatment data will be based on the safety set. The number of active and placebo injections and infusions 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,  $\geq 1$  week,  $\geq 2$  weeks,  $\geq 3$  weeks,  $\geq 4$  weeks,  $\geq 8$  weeks, etc.) will be presented.

Duration of exposure is defined as the time from first dose of study treatment to the time of treatment switch (for subjects who switch treatment) or end of treatment period. For subjects who discontinue this will be the last visit in the corresponding treatment period.

### **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-baseline 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 psoriatic arthritis 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) and the total duration of exposure to psoriatic arthritis therapies previously.

## **9.4 Analysis of the primary variable(s)**

Details of the testing strategy including primary and secondary endpoints are provided in [Section 9.5.1](#).

### **9.4.1 Variable**

The primary efficacy variable will be ACR20 response at Week 24. The analysis of the primary efficacy variable will be based on the FAS. Primarily, CRP will be used instead of ESR to calculate ACR response; ESR will only be used in the event CRP is missing.

### **9.4.2 Statistical model, hypothesis, and method of analysis**

The statistical hypothesis for ACR20 being tested is that there is no difference in the proportion of subjects fulfilling the ACR20 criteria at Week 24 in any of the secukinumab regimens versus placebo regimen.

Let  $p_j$  denote the proportion of ACR20 responders at Week 24 for treatment regimens  $j, j=0, 1, 2$ , where

- 0 corresponds to placebo regimen,
- 1 corresponds to secukinumab 75 mg s.c.,
- 2 corresponds to secukinumab 150 mg s.c.,

In statistical terms,  $H_j: p_j = p_0$ ,  $H_{Aj}: p_j \neq p_0$ , for the  $j^{\text{th}}$  secukinumab regimen, i.e.

$H_1$ : secukinumab 75 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24

$H_2$ : secukinumab 150 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24

The primary endpoint of ACR20 at Week 24 will be analyzed via logistic regression with treatment and TNF-alpha inhibitor status as factors and weight as a covariate. Odds ratios will be computed for comparisons of secukinumab regimens versus placebo regimen utilizing the logistic regression model fitted.

For subjects meeting the criteria for early escape at Week 16, their ACR20 will be set to non-response at Week 24. This applies for all three treatment regimens in order to minimize bias.

### 9.4.3 Handling of missing values/censoring/discontinuations

Missing data for ACR20 response and other binary efficacy variables (e.g. ACR50, ACR70, HAQ-DI response, etc.) for data up to 1-year (week 52) will be handled as follows:

1. Subjects who drop out of the trial for any reason will be considered non-responders from the time they drop out through week 52.
2. 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 baseline and at the specific time point will be classified as non-responders.

Continuous variables (e.g. ACR components, DAS, 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-baseline 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.

Data collected after Week 52 will be presented as 'observed case'; i.e. all available data for each time point will be included in the analyses.

In general, the handling of data for subjects who meet rescue criteria at Week 16 will be handled in the following fashion:

- For binary endpoints, subjects will be considered as non-responders. This will be done for all treatment regimens in order to minimize bias.
- For continuous endpoints, the goal of the analyses would be to estimate what would have happened if the subjects had stayed on the original treatment. Thus, the data collected after the subject switches to secukinumab will be treated as missing for placebo subjects and will be analyzed using a mixed-effects repeated measures model (MMRM) which is valid under the missing at random (MAR) assumption. For secukinumab subjects, the actual values will be used in the analysis.

#### 9.4.4 Supportive analyses

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

In order to determine the robustness of the logistic regression model used for the primary analysis, ACR20 response at Week 24 will also be evaluated using a non-parametric regression (Koch et. al 1998) model with the same independent variables as the logistic regression model

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:

- Multiple imputation
- Observed data analysis

### 9.5 Analysis of secondary variables

#### 9.5.1 Secondary variables

##### Testing strategy

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

Primary objective (as described in [Section 9.4](#)):

- H<sub>1</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24
- H<sub>2</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24

Secondary objectives:

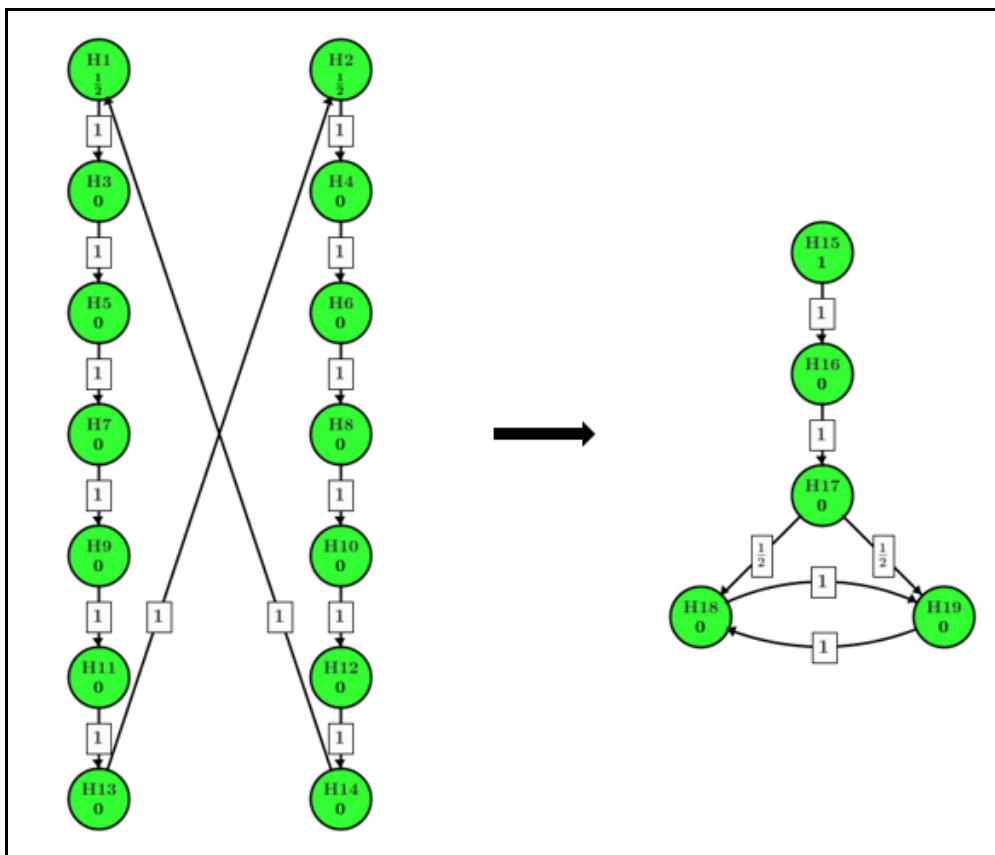
- H<sub>3</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to PASI75 response at Week 24 in the subgroup of subjects who have  $\geq 3\%$  skin involvement with psoriasis
- H<sub>4</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to PASI75 response at Week 24 in the subgroup of subjects who have  $\geq 3\%$  skin involvement with psoriasis
- H<sub>5</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to PASI90 response at Week 24 in the subgroup of subjects who have  $\geq 3\%$  skin involvement with psoriasis
- H<sub>6</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to PASI90 response at Week 24 in the subgroup of subjects who have  $\geq 3\%$  skin involvement with psoriasis
- H<sub>7</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for DAS28-CRP at Week 24



- H<sub>8</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for DAS28-CRP at Week 24
- H<sub>9</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for SF36-PCS at Week 24
- H<sub>10</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for SF36-PCS at Week 24
- H<sub>11</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at Week 24
- H<sub>12</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at Week 24
- H<sub>13</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to ACR50 response at Week 24
- H<sub>14</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to ACR50 response at Week 24
- H<sub>15</sub>: Secukinumab pooled regimen (75 mg and 150 mg s.c.) is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24
- H<sub>16</sub>: Secukinumab pooled regimen (75 mg and 150 mg s.c.) is not different to placebo regimen with respect to presence of dactylitis at Week 24 in the subset of subjects who have dactylitis at baseline
- H<sub>17</sub>: Secukinumab pooled regimen (75 mg and 150 mg s.c.) is not different to placebo regimen with respect to presence of enthesitis at Week 24 in the subset of subjects who have enthesitis at baseline
- H<sub>18</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24
- H<sub>19</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24

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

**Figure 9-1 Testing strategy**



The family-wise error will be set to  $\alpha=5\%$  and it will be controlled with the proposed hierarchical testing strategy. With this hierarchical testing approach, the hypotheses will be separated into two families, hypotheses  $H_1 \sim H_{14}$  will be the first family and hypotheses  $H_{15} \sim H_{19}$  will be the second family. The second family hypotheses will be tested only when all hypotheses in the first family have been rejected. Each of the hypotheses ( $H_1$  and  $H_2$ ) for the primary objective (based on signs and symptoms at week 24) for each secukinumab regimen versus placebo will be tested simultaneously at  $\alpha/2$ . If at least one of  $H_1$  and/or  $H_2$  are/is rejected, then  $H_3$  and/or  $H_4$ , respectively, is tested. If at least one of  $H_3$  and/or  $H_4$  is rejected, the hypothesis  $H_5$  and/or  $H_6$ , is tested, respectively. Similar process applies until  $H_{13}$  and  $H_{14}$ . Once all hypotheses within the first family for a secukinumab regimen are rejected, then the respective  $\alpha/2$  can be passed on to the other regimen's hypotheses within the family, if they are not already rejected at  $\alpha/2$ . Only when all  $H_1 \sim H_{14}$  are rejected, the objective on joint structure endpoint at Week 24 for testing pooled secukinumab doses versus placebo ( $H_{15}$ ) will be tested at  $\alpha$ . If  $H_{15}$  is rejected, then  $H_{16}$  is tested at  $\alpha$ . Similarly if  $H_{16}$  is rejected, then  $H_{17}$  is tested at  $\alpha$ . If these pooled hypotheses are all rejected, then hypotheses concerning individual regimens of secukinumab versus placebo ( $H_{18}$  and  $H_{19}$ ) can be tested for a particular regimen at  $\alpha/2$ . Once the hypothesis of structure damage for a secukinumab regimen is rejected, then the respective  $\alpha/2$  can be passed on to the other regimen's hypothesis, if it is not already rejected at  $\alpha/2$ . Of note, in the description above, rejection of a hypothesis refers to rejection

of the two-sided hypothesis; however the level of a rejected hypothesis is only passed on according to the graphical procedure for the test of another hypothesis if the treatment effect is in favor of secukinumab.

### **PASI 75 and PASI 90 response**

PASI 75 response and PASI 90 at Week 24 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.

### **Changes in DAS28-CRP**

Between-treatment differences in the change from baseline in DAS28-CRP will be compared by means of a mixed model repeated measures (MMRM) with treatment regimen, analysis visit, and TNF-alpha inhibitor status as factors, and weight and baseline as continuous covariates. Treatment by analysis visit and baseline 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 secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

### **SF-36 PCS**

The analysis of SF-36 is described in [Section 9.5.4](#).

### **Physical function (HAQ-DI)**

Between-treatment differences in the change in HAQ-DI 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 baseline HAQ-DI score as continuous covariates. Treatment by analysis visit and baseline 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 secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

### **ACR50 at Week 24**

Response at Week 24 to ACR50 in the FAS will be evaluated using a logistic regression model with treatment and randomization stratum (TNF $\alpha$  status -naive or IR) as factors and weight as a covariate.

### **Joint/bone structural damage at Week 24**

The change at Week 24 from baseline van der Heijde total modified Sharp score will be evaluated using a non-parametric ANCOVA model with treatment regimen and TNF-alpha inhibitor status as factors, and weight and baseline van der Heijde total modified Sharp score as covariates. The pooled secukinumab regimens (75 mg s.c. and 150 mg s.c.) will be

compared to placebo, then each of the secukinumab regimens will be compared versus the placebo regimen via pairwise comparisons.

For subjects who meet the criteria for early escape at Week 16 and subjects who discontinue the study prior to Week 24, linear extrapolation will be used to impute the value at Week 24. If baseline or all post-baseline total modified Sharp score/s is/are missing for a subject, the subject will be excluded from the analyses.

### **Dactylitis at Week 24**

Presence of dactylitis at Week 24 in the subset of subjects who have dactylitis at baseline will be evaluated using a logistic regression model with treatment and randomization stratum (TNF $\alpha$  status -naive or IR) as factors and weight as a covariate.

### **Enthesitis at Week 24**

Presence of enthesitis at Week 24 in the subset of subjects who have enthesitis at baseline will be evaluated using a logistic regression model with treatment and randomization stratum (TNF $\alpha$  status -naive or IR) as factors and weight as a covariate.

## **9.5.2 Exploratory efficacy variables**

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

- HAQ-DI response
- Major clinical response by Week 52 and 104
- Joint/bone structural damage at Week 52 and 104
- Evidence of no disease progression at Week 24, 52 and 104
- PsARC, ACR20/50/70 response over time
- DAS28 remission, low disease activity, EULAR response at Week 24 and over time
- Minimal disease activity
- ACR components
  - Changes in tender joint counts over time
  - Change in swollen joint counts over time
  - Change in Patient's global assessment in disease activity
  - Change in Physician's global assessment in disease activity
  - Change in PsA Pain
  - Change in HAQ-DI over time
  - Change in erythrocyte sedimentation rate (ESR)
  - Change in high-sensitivity C-reactive protein (hsCRP)
- PASI 75, PASI 90, and IGA 0/1 response over time
- Target lesion score
- mNAPSI
- LDI and dactylitis count
- LEI-4

Between-treatment comparisons for binary variables in the FAS population (e.g. PsARC, ACR20, etc.) at individual analysis visits will be evaluated using a logistic regression model with treatment and TNF-alpha inhibitor status as factors and baseline score (if appropriate) and weight as covariates.

Continuous variables (e.g. change from baseline in PsA pain) will be evaluated using a mixed-effect model repeated measures (MMRM) with treatment regimen, TNF-alpha inhibitor status, and analysis visit as factors and weight and baseline score as continuous covariates. Treatment by analysis visit and baseline 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 secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits. Variables such as hsCRP whose distribution is not anticipated to be normal will be transformed and analyzed on the log<sub>e</sub> scale.

### **Joint/bone structural damage at Week 52 and 104**

Observed joint/bone structure data at Week 52 will be compared between subjects randomized at baseline to secukinumab regimen (pooled from 2 secukinumab regimens) and placebo followed by secukinumab regimen. The change from baseline to Week 52 will be evaluated using a non-parametric ANCOVA model utilized for Week 24 and including randomization strata as a covariate.

As sensitivity analysis, for subjects with missing modified Sharp score values at Week 52, their Week 52 value will be imputed by linear extrapolation from baseline, Week 16 and Week 24, and at subject discontinuation visit (if subject discontinued prior to Week 52) to Week 52.

Summary statistics of observed data at Week 52 will be provided for each treatment regimens: secukinumab 75 mg, secukinumab 150 mg, placebo escape or switch to secukinumab 75 mg at Week 16 or 24, placebo escape or switch to secukinumab 150 mg at Week 16 or 24. Summary statistics include mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum.

Observed Joint/bone structure data at Week 104 will be summarized by treatment group. In addition, the change from week 52 will also be summarized within treatment regimen.

### **Evidence of no disease progression at Week 24, 52 and 104**

The proportion of subjects without disease progression will be defined as those subjects who have a change in van der Heijde total modified Sharp score at Week 24 relative to baseline  $\leq 0$ . The proportion of subjects without disease progression at Week 24 will be evaluated using a logistic regression model with treatment group and randomization strata, as factors, weight and baseline van der Heijde total modified Sharp score as covariates.

The proportion of subjects without disease progression at Week 52 and 104 will be evaluated in the same manner. At week 104, the proportion of subjects with disease progression from week 52 will also be examined.

## **EULAR response at Week 24 and over time**

Based on the EULAR response criteria (good responder, moderate responder, and non-responder) as determined based on the value of DAS28-CRP achieved and the magnitude of change from baseline, between-treatment differences in EULAR response at Week 24 and other analysis visits will be evaluated using a proportional odds regression model with treatment group and randomization strata as factors and weight and baseline DAS28-CRP score as covariates. Frequency tables will also be presented to show the response rate over time up to Week 24 and Week 52, as appropriate.

## **Magnetic Resonance Imaging**

MRI Analysis will be based on the subjects who have MRI performed at selected centers.

The change in synovitis between Week 24 and baseline will be evaluated using a nonparametric ANCOVA model with treatment regimen as a factor, weight and baseline erosion score as covariates. Pair-wise comparison versus placebo will be made for each of the secukinumab regimens. Tenosynovitis, periarticular inflammation, bone edema/osteitis, bone erosion, bone proliferation, and joint space narrowing will be evaluated in the same manner.

For subjects with missing data at Week 24, linear extrapolation will be used to impute missing data. In order to minimize bias, the extrapolation will use baseline and week 12. Change from baseline will be summarized by analysis visit with summary statistics including mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum.

## **LEI-4**

In this study, the lateral condyle femur L + R data were collected instead of required medial condyle femur L + R. Therefore, a 4-site LEI (LEI-4, i.e. score with the four correct sites: lateral epicondyle humerus L + R and proximal achilles L + R) will be summarized by treatment group and visit. Change from baseline in the 4-site LEI will be analyzed using a nonparametric ANCOVA model with treatment regimen and randomization strata as factors, weight and baseline score as covariates. Pair-wise comparison versus placebo will be made for each of the secukinumab regimens by visit.

### **9.5.3 Safety variables**

#### **Adverse events**

Treatment emergent adverse events (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized.

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 adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event 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. Serious adverse events will also be summarized.

These summaries may be presented separately by study periods.

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

Separate summaries will be provided for death, serious adverse event, and other significant adverse events leading to discontinuation.

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

When adjudication is required of major cardiovascular events (MACE), a summary of those types of events as reported by the investigator and confirmed by adjudication will be provided.

### **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 baseline and post baseline.

For each parameter, the maximum change from baseline within each study period will be evaluated analogously.

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment group. Shifts will be presented by visit as well as for most extreme values post-baseline.

### **Immunogenicity**

A listing of immunogenicity (anti-AIN457 antibodies) will be provided.

### **Vital signs**

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

### **ECG**

Summary statistics will be presented for ECG variables by visit and treatment group. Qualitative changes will be summarized.

#### **9.5.4 Health-related Quality of Life**

The PsAQoL will be evaluated for FAS subjects where data are available. All Health-related Quality of Life will be evaluated based on FAS.

##### **EQ-5D**

The number and percentage of subjects in each of the three categories for each question will be presented by visit and treatment group.

Summary statistics will be shown for the health state assessment by visit and treatment group.

For the change in EQ-5D overall health state (VAS), between-treatment differences in the change in EQ-5D overall health state (VAS) will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline EQ-5D overall health state (VAS) and weight as continuous covariates. Treatment by analysis visit and baseline EQ-5D overall health state (VAS) 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.

##### **SF-36**

The following variables will be evaluated:

- SF-36 domain scores.
- SF-36 PCS and MCS scores.
- SF-36 PCS responder (improvement of  $\geq 2.5$  points, [Lubeck 2004](#))

Between-treatment differences in the change from baseline for SF-36 summary scores (PCS/MCS) will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline SF-36 score and weight as continuous covariates. Treatment by analysis visit and baseline 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.

In the responder analyses, treatment groups will be compared with respect to response to treatment using a logistic regression model with treatment and TNF-alpha inhibitor status as factors, baseline SF-36 summary score and weight as covariates. Odds ratios with corresponding 95% confidence intervals will be estimated in addition.

Individual SF-36 domain scores will be summarized.

##### **FACIT-Fatigue**

Between-treatment differences in the change from baseline for FACIT-Fatigue scores will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline and weight as continuous



covariates. Treatment by analysis visit and baseline 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.

### **Dermatology Life Quality Index**

Between-treatment differences in the change from baseline for DLQI will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline and weight as continuous covariates. Treatment by analysis visit and baseline 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.

### **PsAQoL**

Between-treatment differences in the change from baseline for PsAQoL scores will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline and weight as continuous covariates. Treatment by analysis visit and baseline 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.

### **WPAI-GH**

Summary statistics will be shown for the WPAI-GH assessment by visit and treatment group.

### **9.5.5 Pharmacokinetics**

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

#### **Pharmacokinetic variables**

The following pharmacokinetic parameter will be determined: C<sub>min,ss</sub>. Individual concentrations will be listed.

Biofluid concentrations will be expressed in µg/ml. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the Limit of Quantification will be treated as zero in summary statistics for concentration data only.

C<sub>min,ss</sub> will be determined using Phoenix.

During modeling of the pharmacokinetics of secukinumab, the broad principles outlined in the FDA Guidance for Industry: Population Pharmacokinetics will be followed.

## Statistical methods for pharmacokinetic analyses

All completed subjects with quantifiable PK measurements of secukinumab will be included in the PK data analysis. Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. PK concentrations will be summarized by visit and treatment group. In addition to mean, standard deviation, coefficient of variation, median and quartiles, the geometric mean and geometric coefficient of variation and n(log) will be presented.

### 9.5.6 Pharmacogenetics

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests (chi-square tests, ANCOVAs, linear and logistic regression) are used for the analyses. Additional data, from subsequent clinical trials, are often needed to confirm associations. Alternatively, if the numbers of subjects enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

### 9.5.7 Biomarkers

Soluble marker panel studies investigate differences in the level of expression of proteins or peptides between individuals in a given biofluid. The goal of such studies is to allow the identification of potential protein or peptide biomarkers of drug action or disease, and to better understand the associated underlying molecular mechanisms. By applying statistical analysis methods (e.g. principal component analysis) between subject groups, distinct study time points, or between study groups from other clinical trials, it may be possible to identify patterns which are associated with disease state or response to drug treatment. However, the exact type of data analysis method will depend on the type of data obtained in the study and thus the analysis of this data will be data driven.

### 9.5.8 PK/PD

An indirect response model, driven by study treatment concentration, will be used to characterize the time course of efficacy response. Further details of the modeling approach will be specified in a modeling plan.

## 9.6 Sample size calculation

The original power calculations used in the protocol have been updated to incorporate more recent published data in the PsA population. In addition, the statistical hierarchy (primary plus ranked secondary variables) was expanded to include more endpoints important in the treatment of psoriatic arthritis patients. No adjustment was made to the sample size as a result of the updated power calculations; the original sample size of N=200 per treatment regimen was retained. The adjustments to the power calculations and the statistical hierarchy were done before the unblinding of the trial in order to prevent bias.

A 5% two-sided type I error rate will be used to control for type I error. Two secukinumab doses will be tested versus placebo with respect to the primary endpoint (ACR20 response at Week 24), thus the type-I-error will be split to 2.5% two-sided for each comparison. Sample sizes will be based on this type I error assumption.

A placebo response rate of about 25% after 24 weeks was reported for the TNF $\alpha$  inhibitor naïve population in the PSUMMIT I study (McInnes et al 2013), and 15% was reported for the TNF $\alpha$  inhibitor IR population in the PSUMMIT II study (Ritchlin et al 2013). Based on the weighted average, the overall placebo rate is expected to be 22%.

The response on secukinumab is expected to be 55% in the TNF $\alpha$  inhibitor naïve population and 35% in the TNF $\alpha$  inhibitor IR-population. Based on the weighted average, the overall rate on a dose of secukinumab is expected to be 49%.

For the primary endpoint, ACR20 in the overall population, 200 subjects per group would yield approximately 99% power to detect a treatment difference in the response rates between the secukinumab regimens and placebo with the above assumptions (Fisher's exact test, nQuery 7.0).

## 9.7 Power for analysis of secondary variables

Power for secondary variables was calculated using a two-sided 2.5% type I error. With an assumed placebo rate of 7.6% and secukinumab 58.1%, the study is over 99% powered to detect a treatment difference of PASI75 in the full FAS population, assuming 135 subjects per treatment arm (Fisher's exact test, nQuery 7.0). Similarly, with an assumed placebo rate of 5% and secukinumab 44%, the study is over 99% powered to detect a treatment difference of PASI90 in the full FAS population, assuming 135 subjects per treatment arm. It is assumed that about 67.5% of enrolled patients have  $\geq 3\%$  skin involvement with psoriasis. Assumptions of PASI75 and PASI90 rates are based on PSUMMIT I and II studies (McInnes et al 2013 and Ritchlin et al 2013).

A between-treatment difference of 1.31 and standard deviation of 1.34 has been observed for the change from baseline in DAS28-CRP in Golimumab (Kavanaugh et al 2009) for the TNF $\alpha$  inhibitor naïve population. Assuming the difference is half in the TNF $\alpha$  inhibitor IR population, the overall population has a between-treatment difference of 1.12. With these assumptions, the study has approximately over 99% power to detect a difference between secukinumab and placebo (Two group t-test, nQuery Advisor 7.0), assuming 200 subjects per arm.

A standard deviation of approximately 10.1 and a between-treatment difference of 6.32 has been observed for the change from baseline at week 24 in SF36-PCS in Ustekinumab trial (McInnes et al 2013). Using those assumptions, the study has approximately 99% power to detect a difference between secukinumab and placebo (Two group t-test, NQuery Advisor 7.0), assuming 200 subjects per arm.

A standard deviation of approximately 0.5 and a between-treatment difference of 0.25 has been observed for the change from baseline at week 24 in HAQ-DI in Ustekinumab trial (McInnes et al 2013; Ritchlin et al 2012; Ritchlin et al 2013). Using those assumptions, the study has approximately 99% power to detect a difference between secukinumab and placebo (Two group t-test, NQuery Advisor 7.0), assuming 200 subjects per arm.

With an assumed placebo rate of 7.4% (McInnes et al 2013; Ritchlin et al 2012; Ritchlin et al 2013) and secukinumab 25.5%, the study is over 99% powered to detect a between-treatment difference of ACR50 in the full FAS population, assuming 200 subjects per treatment arm (Fisher's exact test, nQuery 7.0).

For structural endpoint, historical data (adalimumab) showed a standard deviation of 1.2 on active treatment and 2.4 on placebo at week 26, and a between-treatment difference of 0.6 for the TNF $\alpha$  inhibitor naïve population (Mease et al 2005). Assuming the between-treatment difference is half in the TNF $\alpha$  inhibitor IR population, the overall population has a between-treatment difference of 0.51. Using the above assumptions, there is 80% power to show statistically significant differences between secukinumab (pooled 400 subjects) and placebo (200 subjects). Individual comparisons between secukinumab and placebo would have 66% power (Satterthwaite t-test, nQuery 7.0).

For the presence of dactylitis at Week 24 in the subset of subjects who have dactylitis at baseline, with an assumed placebo rate of 76% (McInnes et al 2013) and secukinumab 57%, there is about 89% power to show statistically significant difference between secukinumab (pooled 200 subjects) and placebo (100 subjects), assuming 50% subjects have dactylitis at baseline (Fisher's exact test, nQuery 7.0).

For the presence of enthesitis at Week 24 in the subset of subjects who have enthesitis at baseline, with an assumed placebo rate of 81% (McInnes et al 2013) and secukinumab 65%, there is about 87% power to show statistically significant difference between secukinumab (pooled 240 subjects) and placebo (120 subjects), assuming 60% subjects have enthesitis at baseline (Fisher's exact test, nQuery 7.0).

## 9.8 Interim Analysis

The Week 52 analysis will be performed after all subjects have completed the Week 52 visit. For this analysis, all subjects will have completed the assessments related to the primary and secondary objectives. Thus, no adjustment will be made to the type I error rate for this analysis and an interim clinical study report will be produced.

## **10 Ethical considerations**

### **10.1 Regulatory and ethical compliance**

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

### **10.2 Informed consent procedures**

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

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

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

The study includes an optional pharmacogenetic component which requires a separate signature if the subject agrees to participate. It is required as part of this protocol that the Investigator presents this option to the subject. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these pharmacogenetic assessments will in no way affect the subject's ability to participate in the main research study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or ethics committee approval will be obtained.

### **10.3 Responsibilities of the investigator and IRB/IEC**

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. 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 Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

### **10.4 Publication of study protocol and results**

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

## **11 Protocol adherence**

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the 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 it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

### **11.1 Protocol Amendments**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for subject safety may be implemented prior to IRB/IEC approval. 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 within 10 working days.

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## 13 Appendices

### 13.1 Appendix 1: Clinically notable laboratory values and vital signs

#### Safety Analyses: Expanded Limits and Notable Criteria

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.

Final Harmonization			
Laboratory Variable	Notable Criteria		
	Standard Units	SI Units	
<b>LIVER FUNCTION AND RELATED VARIABLES</b>			
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	
<b>RENAL FUNCTION, METABOLIC AND ELECTROLYTE VARIABLES</b>			
Creatinine (serum)	>2 x ULN <sup>1)</sup>	>2 x ULN <sup>1)</sup>	

<sup>1)</sup> The baseline serum creatinine value is the pre-treatment serum creatinine level, which is defined as the creatinine level measured at screening (Visit 1).

#### 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

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

Total score: \_\_\_\_\_

(The CASPAR criteria eCRF will auto-populate the total number of points of the CASPAR criteria met by the subject. If the total score  $\geq 3$ , the subject meets CASPAR criteria for PsA diagnosis.)

<sup>†</sup> Current psoriasis is assigned a score of 2; all other features are assigned a score of 1

### **13.3 Appendix 3: American College of Rheumatology (ACR) Measures and Criteria of Response**

#### **Number of tender joints**

Seventy-eight joints (78) are scored as either tender or not tender: 8 distal interphalangeal, 10 proximal interphalangeal, 10 metacarpophalangeal and 2 first carpometacarpal joints of the hands, 8 distal interphalangeal, 10 metatarsophalangeal and 10 proximal interphalangeal joints of the feet, the 2 wrists, 2 elbows, 2 shoulders, 2 acromioclavicular, 2 sternoclavicular, 2 temporomandibular, 2 hip, 2 knee, 2 talo-tibial, and 2 mid-tarsal joints.

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

#### **Number of swollen joints**

Joints are to be scored as either swollen (1) or not swollen (0). The 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<sup>®</sup>

#### **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:
  - Patient's assessment of pain,
  - Patient's global assessment of disease activity,
  - Physician's global assessment of disease activity,
  - Health Assessment Questionnaire (HAQ<sup>®</sup>) score,

- C-reactive protein (CRP)/Erythrocyte Sedimentation Rate (ESR).

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

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

Reference: ([Felson 1995](#))

### **13.4 Appendix 4: The Psoriatic Arthritis Response Criteria (PsARC)**

The PsARC represent a composite measure of psoriatic arthritis disease severity and include the following 4 measures:

1. Patient global assessment of disease activity (improvement of 1 on a 5-point Likert scale is required for a response)
2. Physician global assessment of disease activity (improvement of 1 on a 5-point Likert scale is required for a response)
3. Joint pain (reduction of 30% or more in total score, assessing either 68 or 78 joints, using a 4-point scale is required for a response)
4. Joint swelling (reduction of 30% or more in total score, assessing either 68 or 78 joints, using a 4-point scale is required for a response)

In order to be a 'PsARC responder' patients must achieve improvement in 2 of the above mentioned 4 measures, one of which must be joint pain or swelling, without worsening in any of the 4 measures.

### 13.5 Appendix 5: Disease Activity Score (DAS)

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

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

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

#### The DAS in the clinical trials

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

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

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

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

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

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

$$\text{DAS28} = 0.56 * \text{sqrt}(\text{tender28}) + 0.28 * \text{sqrt}(\text{swollen28}) + 0.70 * \ln(\text{ESR}) + 0.014 * \text{GH}$$

The DAS28 provides you with a number on a scale from 0 to 10 indicating the current activity of the rheumatoid arthritis of your patient. A DAS28 above 5.1 means high disease activity

whereas a DAS28 below 3.2 indicates low disease activity. Remission is achieved by a DAS28 lower than 2.6 (comparable to the ARA remission criteria).

### **Disease Activity Scores using C-reactive protein**

C-reactive protein (CRP) may be used as an alternative to ESR in the calculation of the DAS or DAS28, using the formulas below. CRP is a more direct measure of inflammation than ESR, and it is more sensitive to short-term changes (Kushner 1991). CRP production is associated with radiological progression in RA (Van Leeuwen 1993), and is considered at least as valid as ESR to measure RA disease activity (Mallya 1982, Wolfe 1997). Another advantage of determination of CRP is that waiting time for the laboratory result is shorter and that in case of multicenter studies a central laboratory can be used.

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

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

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



### 13.6 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 scaling, which are each rated on a scale of 0 to 4. The scoring system for the signs of the disease (erythema, induration, and 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:

$$\text{PASI} = 0.1 (\text{Eh} + \text{Ih} + \text{Sh}) \text{Ah} + 0.3 (\text{Et} + \text{It} + \text{St}) \text{At} + 0.2 (\text{Eu} + \text{Iu} + \text{Su}) \text{Au} + 0.4 (\text{El} + \text{Il} + \text{Sl}) \text{Al}$$

where E = erythema, I = induration, S = scaling, and A = area

## PASI Scoring Worksheet

	Head	Upper extremities	Trunk	Lower extremities
1. Redness†				
2. Thickness†				
3. Scale†				
4. Sum of rows 1, 2, and 3				
5. Area score‡				
6. Score of row 4 x row 5 x the area multiplier	Row 4 x row 5 x 0.1	Row 4 x row 5 x 0.2	Row 4 x row 5 x 0.3	Row 4 x row 5 x 0.4
<b>7. Sum row 6 for each column for PASI score</b>				
a. Divide body into four areas: head, arms, trunk to groin, and legs to top of buttocks.				
b. Generate an average score for the erythema, thickness, and scale for each of the 4 areas (0=clear, 1-4=increasing severity).				
c. Sum scores of erythema, thickness, and scale for each area.				
d. Generate a percentage for skin covered with psoriasis for each area and convert that to a 0-6 scale. ‡				
e. Multiply score of item c above times item d above for each area and multiply that by 0.1, 0.2, 0.3 and 0.4 for head, arms, trunk, and legs, respectively.				
f. Add these scores to get the PASI score.				
† Erythema, thickness, and scale are measured on a 0-4 scale (none, slight, mild, moderate, severe)				
‡Area scoring criteria (score: % involvement)				
0: 0% (clear)				
1: <10%				
2: 10-<30%				
3: 30-<50%				
4: 50-<70%				
5: 70-<90%				
6: 90-100%				

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

## 13.7 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.

### 13.8 Appendix 8: Standard reference table for the LDI

**Table – hands (in cm)**

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

**Table – feet (in cm)**

<b>Digit</b>	<b>Men</b>	<b>Women</b>
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

## 13.9 Appendix 9: Guidelines for administering PRO questionnaires

### Before trial begin

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) and the digital pen
- 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
- Subjects should initial and date the last page of the questionnaires
- Also see 'Addressing Problems and Concerns'

### After completion

- Check for completeness and not for content\*
- Check for multiple responses that were made in error
- Data should be transcribed from the completed questionnaire to the appropriate screen on the e-CRF
- File completed questionnaire in the subject study files

*\*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 this

information is as important as any of the other medical information, and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the respondent has filled in the past. If the 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 possibly the investigator. Any response which may directly impact on or reflect their medical condition (e.g. noting of severe depression) will be communicated by the coordinator to the physician.

### **The 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.

Clinical Development

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457F2306

**A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active psoriatic arthritis**

### **RAP Module 3 – Detailed Statistical Methodology**

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## List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALT/GPT	Alanine aminotransferase/glutamic pyruvic transaminase
ANA	Anti-nuclear antibodies
Anti-CCP	Anti-cyclic citrullinated peptide
AS	Ankylosing Spondylitis
AST/GOT	Aspartate aminotransferase/glutamic oxaloacetic transaminase
BME	Bone Marrow Edema
BMI	Body Mass Index
BSL	Baseline
CASPAR	CIASSification criteria for Psoriatic ARthritis
CFR	Code of Federal Regulations (US)
CRF	Case Report/Record Form
CRD	Clinical Research and Development
CPO	Country Pharma Organization
CRO	Contract Research Organization
CRP/hsCRP	C-reactive protein / high sensitivity C-reactive protein
CSR	Clinical Study Report
CTEP	Cancer Therapy Evaluation Program
DAS	Disease Activity Score
DMARD	Disease Modifying Antirheumatic Drug
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic acid
DS&E	Drug Safety and Epidemiology
dsDNA	Anti-double stranded DNA antibodies
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EMA/EMEA	European Medicines (Evaluation) Agency
EULAR	European League Against Rheumatism

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ESR	Erythrocyte Sedimentation Rate
FACIT-Fatigue <sup>®</sup>	Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GEE	Generalized estimating equation
HAQ-DI <sup>®</sup>	Health Assessment Questionnaire – Disability Index
HIV	Human Immunodeficiency Virus
HRQoL	Health-related Quality of Life
hsCRP	High sensitivity C-Reactive Protein
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGA mod 2011	Novartis Investigator’s Global Assessment modified 2011
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	IntraUterine Device
IUS	IntraUterine System
i.v.	intravenous(ly)
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDI	Leeds Dactylitis Index
LDL	Low Density Lipoprotein
LEI	Leeds Enthesitis Index
LLN	Lower limit of normal
LOCF	Last observation carried forward
LLOQ	Lower Limit of quantification
MCR	Major Clinical Response
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities

---

MRD	Mean relative difference
mmHg	Millimeter mercury
MMP	Matrix Metalloprotease
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PG	Pharmacogenetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PoC	Proof of Concept
PPD	Purified protein derivative
PRN	As required
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
PsAMRIS	Psoriatic Arthritis Magnetic Resonance Imaging Scoring System
PsAQoL	Psoriatic Arthritis Quality of Life questionnaire
QoL	Quality of Life
RA	Rheumatoid Arthritis
RBC	Red Blood Cells
RF	Rheumatoid Factor
SAE	Serious adverse event
s.c.	subcutaneous(ly)
SCR	Screening
SF-36	Medical Outcome Short Form (36) Health Survey
SJC	Swollen Joint Count
SNP	Single Nucleotide Polymorphism
SpA	Spondyloarthritides
SWFI	Sterile water for injection
t.i.d.	ter in die, three times daily
TJC	Tender Joint Count
TNF	Tumor necrosis factor

TNF-IR	TNF $\alpha$ Inhibitor Incomplete Responders
ULN	Upper limit of normal
US	Unites States of America
VAS	Visual Analog Scale
WBC	White Blood Cells
WHO	World Health Organization
WPAI-GH	Work Productivity and Activity Impairment–General Health questionnaire



## **1 Introduction**

Data will be analyzed by Novartis according to the data analysis section 9 of the clinical study protocol. That statistical methodology is described below and any deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section.

## **2 Study Objectives**

The primary objective is to demonstrate the efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo in patients with active PsA based on the proportion of patients achieving an ACR20 response in the entire study population.

The secondary objectives of the study are to demonstrate:

- The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving a PASI75 response in the subgroup of subjects who have  $\geq 3\%$  skin involvement.
- The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving a PASI90 response in the subgroup of subjects who have  $\geq 3\%$  skin involvement.
- The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the DAS28-CRP at Week 24 in the entire study population.
- The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the SF36-PCS at Week 24 in the entire study population.
- The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the HAQ-DI at Week 24 in the entire study population.
- The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving an ACR50 response in the entire study population.
- The improvement (change) from baseline to Week 24 on secukinumab pooled regimen (75 mg and 150 mg s.c.) is superior to placebo for joint/bone structural damage (van der Heijde modified total Sharp score) in the entire study population.
- The efficacy of secukinumab pooled regimen (75 mg and 150 mg s.c.) at Week 24 is superior to placebo based on the proportion of subjects with dactylitis in the subset of subjects who have dactylitis at baseline.
- The efficacy of secukinumab pooled regimen (75 mg and 150 mg s.c.) at Week 24 is superior to placebo based on the proportion of subjects with enthesitis in the subset of subjects who have enthesitis at baseline.
- The improvement (change) from baseline to Week 24 on secukinumab 75 or 150 mg is superior to placebo for joint/bone structural damage (van der Heijde modified total Sharp score) in the entire study population.

Furthermore, additional aspects of efficacy, safety and tolerability of secukinumab will be investigated.

### **3 Data presentation**

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

If not otherwise specified, p-values and confidence intervals will be two-sided.

Unless otherwise stated, the level of significance will be set to 5% (two-sided, family-wise type-I-error).

Data analyses will be presented by treatment regimen. Efficacy and safety data for the placebo-controlled period will be presented by the following 3 treatment groups. Subjects may be included in more than one treatment group for some analyses (e.g. exposure-adjusted adverse events over the entire treatment period). These treatment groups represent the regimens subjects will be eligible to be randomized to for the first 24 weeks of the study.

- Secukinumab regimen 1: secukinumab i.v. (10mg/kg) at BSL, Week 2 and Week 4 then secukinumab 75 mg s.c. starting at Week 8 and injected every 4 weeks
- Secukinumab regimen 2: secukinumab i.v. (10mg/kg) at BSL, Week 2 and Week 4 then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks
- Placebo regimen: Placebo i.v. at BSL, Week 2 and Week 4 then placebo s.c. starting at Week 8 and injected every 4 weeks

Note that the treatment groups above 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 4.2](#) for details).

#### **Comparative efficacy data**

Comparative efficacy analyses (i.e. inferential efficacy comparisons with placebo or active comparator) will focus on the time period when both active drug and the placebo are given in a manner suitable for making comparisons (e.g. double-blind). For AIN457F2306 this is the first 24-weeks of treatment. Comparative efficacy will be performed based on the FAS population using the randomized treatment. After week 24, the active secukinumab regimens will be compared using confidence intervals on the FAS population using treatment sequence.

#### **Efficacy data following rescue/re-randomization**

Data will also be presented after Week 24, by a combination of the 'original' and 'switch' treatment groups and will be referred to as treatment sequence. These treatment sequences represent the treatment combinations the subjects experience over the course of the entire trial in case of rescue or re-randomization.

All listings will be presented by treatment sequence.

## **4 Subjects and treatments**

### **4.1 Analysis Sets**

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

**Randomized set:** The randomized set will be defined as all subjects who were randomized. Unless otherwise specified, mis-randomized subjects (mis-randomized in IWRS/IVRS/IXRS) 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 patients 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 actual stratum, if stratified randomization is used.

**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.

### **4.2 Treatment groups**

The summaries by treatment will be performed by the randomized treatment or treatment sequence. For some safety summaries (e.g. exposure-adjusted) the 'switch' treatment may be summarized separately

- Randomized treatment:
  - AIN457 10 mg/kg - 75 mg
  - AIN457 10 mg/kg - 150 mg
  - Placebo
- Treatment sequence:
  - AIN457 10 mg/kg - 75 mg
  - AIN457 10 mg/kg - 150 mg
  - Placebo (non-responder) - AIN457 75 mg
  - Placebo (non-responder) - AIN457 150 mg
  - Placebo (responder) - AIN457 75 mg
  - Placebo (responder) - AIN457 150 mg
- Switch treatments (for placebo patients who cross-over):
  - AIN457 75 mg no load
  - AIN457 150 mg no load

## 5 Subgroup definitions

The primary endpoint(s) and secondary endpoints will be evaluated for TNF-alpha inhibitor status.

## 6 Assessment windows, baseline and post baseline definitions, missing data handling

### Baseline and post-baseline definitions

In general, a *baseline* value refers to the last measurement made prior to administration of the first dose of study treatment. A post-baseline value refers to a measurement taken after the first dose of study treatment.

### Analysis visit windows

*Analysis visit windows* will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are protocol defined scheduled visits around which analysis visit windows were created to cover the complete range of days within the study. The analysis visit windows and rules for dealing with multiple measurements within the windows are described in the [Appendix](#).

## 7 Subject disposition, background and demographic characteristics

### 7.1 Subject disposition

The number of subjects screened will be presented. In addition, the reasons for screen failures will be provided. The number and percentage of subjects in the randomized set who completed the study periods and who discontinued the study prematurely (including the reason for discontinuation) will be presented at the end of each treatment period (Week 52 and Week 104), if appropriate, for each treatment group and all subjects.

The number and percentage of patients who meet the rescue criteria at week 16 will be presented.

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

### 7.2 Background and demographic characteristics

The following common background and demographic variables, if collected, will be analyzed in all studies:

#### Continuous variables:

- Age (which is derived from date of birth and the screening assessment date)

- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)<sup>2</sup>

**Categorical variables:**

- Age categories (<65 years, 65 years and older, 75 years and older)
- Gender
- Race
- Ethnicity

The following disease specific baseline characteristics and history of disease will be summarized as well:

- TNF $\alpha$  history (naive or inadequate responder), ACR components, number of prior biologic PsA therapies, MTX use (yes or no) and dose at baseline, time since first diagnosis of PsA, and psoriasis involvement (proportion of patients with psoriasis of hands and feet, psoriasis of the nail, and target lesion diameter).

Unless otherwise specified, summary statistics will be presented for continuous variables for each treatment group and for all subjects (total) 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 (total) in the randomized set.

## **8 Medical history**

Any condition entered on the *Relevant medical history / current medical conditions* CRF will be coded using the MedDRA dictionary. They will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. Summaries for cardiovascular medical history and psoriasis history will be provided as well.

Smoking history will be summarized by treatment group.

Chest x-ray (screening) results will be listed.

Unless otherwise specified, analyses will be based on the randomized set.

## **9 Study medication**

The analysis of study treatment data will be based on the safety set. The number of active and placebo infusions and injections will be summarized 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,  $\geq 1$  week,  $\geq 2$  weeks,  $\geq 3$  weeks,  $\geq 4$  weeks,  $\geq 8$  weeks, etc.) will be presented.

Duration of exposure will be defined as the time from first dose of study treatment to the time of treatment switch (for subjects who switch treatment) or end of treatment period (whichever is first). For subjects who discontinue, this will be the subject's last visit in the corresponding treatment period.

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

Duration of exposure (100 subject years) = duration of exposure (years) / 100

The analyses of duration of exposure described above will be done for the entire study treatment period.

## **10 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-baseline 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 surgeries and procedures will be summarized by primary system organ class and MedDRA preferred term.

The number and percentage of subjects receiving prior and concomitant psoriatic arthritis 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) and the total duration of exposure to psoriatic arthritis therapies previously.

Prior or concomitant medication will be identified by comparing recorded or imputed start and end dates of medication taken to the reference start date. Further rules will be given in RAP Module 8.

## **11 Efficacy evaluation**

### **11.1 Description of efficacy variables**

#### **ACR 20/50/70**

ACR20 is a binary response variable defined for each subject. A subject will be considered a responder according to ACR20 criteria if he/she has at least (i.e.,  $\geq$ ):

- 20% improvement from baseline in tender 78-joint count
- 20% improvement from baseline in swollen 76-joint count
- 20% improvement from baseline in at least 3 of the following 5 measures:
  - Patient's assessment of PsA pain (VAS 100 mm)
  - Patient's global assessment of PsA disease activity (VAS 100 mm)
  - Physician's global assessment of PsA disease activity (VAS 100 mm)

- Patient self-assessed disability (Health Assessment Questionnaire [HAQ©] score)
- Acute phase reactant (C-reactive protein [hsCRP]) **or** Erythrocyte sedimentation rate (ESR).

In the definition above, the *baseline* value refers to the last measurement made prior to administration of the first dose of study treatment.

The primary endpoint is the proportion of subjects achieving ACR20 at Week 24. Primarily, CRP will be used to calculate ACR response: ESR will only be used in the event CRP is missing.

ACR50 and ACR70 are defined in the same way as ACR20 by replacing the 20% with 50% and 70% improvement from baseline, respectively.

ACRn represents the percent improvement on the continuous scale and from ACRn one can directly calculate ACR20, ACR50, and ACR70 using the appropriate cutoffs. This variable is defined as:

$ACRn = \min(x_1, x_2, x_3)$ , where

$x_1$  = % improvement from baseline in tender 68-joint count

$x_2$  = % improvement from baseline in swollen 66-joint count

and  $x_3 = 3^{\text{rd}}$  largest value of  $x_4, x_5, x_6, x_7, x_8$  where,

$x_4$  = % improvement from baseline in Patient's assessment of PsA pain (VAS 100 mm)

$x_5$  = % improvement from baseline in Patient's global assessment of PsA disease activity (VAS 100 mm)

$x_6$  = % improvement from baseline in Physician's global assessment of PsA disease activity (VAS 100 mm)

$x_7$  = % improvement from baseline in Patient self-assessed disability (Health Assessment Questionnaire [HAQ©] score)

$x_8$  = % improvement from baseline in Acute phase reactant (C-reactive protein [hsCRP]) **or** Erythrocyte sedimentation rate (ESR)

ACRn can be computed even if up to two values of  $x_4, x_5, x_6, x_7, x_8$  are missing. ACRn, theoretically, can not be computed, if one or both of  $x_1, x_2$  is/are missing OR more than three values of  $x_4, x_5, x_6, x_7, x_8$  are missing.

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

The Health Assessment Questionnaire (HAQ©) 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 (Health Assessment Questionnaire – Disability Index), 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].

Scoring for the eight functional categories and overall disability index scoring will be performed as follows:

There are eight categories; first score within each category:

- Dressing and Grooming, includes items 1 and 2
- Arising, includes items 3 and 4
- Eating, includes items 5, 6 and 7
- Walking, includes items 8 and 9
- Hygiene, includes items 10, 11, and 12
- Reach, includes items 13 and 14
- Grip, includes items 15, 16 and 17
- Activities, includes items 18, 19, and 20

The score for each category will be the single response within the category with the highest score (greatest difficulty). For example, in the "Eating" category, there are two answers (one for each item). If "Cut your food with a knife or fork" is marked as "3" and "Lift a full cup or glass to your mouth" is marked as "0", then the score for the "Eating" category would be "3" (the response indicating the greatest difficulty within the category). If a component question is left blank or the response is too ambiguous to assign a score, then the score that that category will be determined by the remaining completed question(s). However, if **any** "aids or devices" and/or "help from another person" items at the bottom of each page are checked, the category to which they apply will be adjusted upward to "2". If the basic score is **already** "2" or "3", the score remains unchanged. "Aids or devices" and "help from another person" can **only** change a category's score to "2"; they do **not** change the score to a "1" or a "3".

The score for the disability index will be the mean of the eight category scores. If more than two of the categories, or 25%, are missing, scale will not be scored. Otherwise, divide the sum of the categories by the number of answered categories. The higher score indicates greater disability.

**HAQ-DI response** is defined by an improvement of at least 0.3 score points compared to baseline.

### **Joint/bone structural damage**

The primary score for analyses will be total van der Heijde modified Sharpe (vdH-S) score (van der Heijde 1999), but the erosion score and joint space narrowing score will be analyzed in similar fashion.

Erosions will be assessed each hand (20 locations per hand) and each foot (6 locations per foot). The maximum erosion score is 200 for all 40 hand locations, and 120 for all 12 feet locations. Thus, the total possible erosion score is 320.



Joint space narrowing (JSN) will be assessed in each hand (20 locations per hand) and foot (6 locations per foot). The maximum score is 160 for all 40 hand joints, and 48 for all 12 feet joints. Thus, the total possible JSN score is 208.

Pencil-in-cup: Osteolysis of the proximal phalanx and the base of the distal phalanx resulting in a pencil like proximal phalanx covered by cup like base of the distal phalanx. Pencil-in-cup will be scored as "P" where applicable.

Gross Osteolysis: Osteolysis of the phalanx resulting in a loss of the normal joint structure, usually accompanied by shortening of the length of the phalanx. Gross osteolysis will be scored as "G" where applicable.

If a joint or bone is not visible (e.g. poor film quality, missing imaging, severe misalignment, flexion deformity, dislocation) at the timepoint, the individual joint or bone will be coded as Not Visible (N).

If radiographs at the timepoint show a joint or bone with surgical fusion, replacement (prosthesis), or amputation, then the joint or bone will be scored Surgically Modified (S).

To obtain the total vdH-S score, scores for erosions and JSN in both the hands and feet will be added together. Any "P" or "G" will be considered the maximal score for the feature (erosions and JSN) per location in the calculation of the total vdH-S score. Any "N" or "S" will be considered null in the calculation of the total vdH-S score. The range of scores is 0 ~ 528.

If the scores are missing for some locations, let ES denote the erosion score and JSNS denote the joint space narrowing score, the total score will be calculated as follows:

$$12*\text{avg}(\text{feet ES}) + 12*\text{avg}(\text{feet JSNS}) + 40*\text{avg}(\text{hands ES}) + 40*\text{avg}(\text{hands JSNS})$$

### **Major clinical response**

Major clinical response is defined as continuous six-months of ACR70 response for a subject.

### **DAS28, low disease activity and remission**

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

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

The following 28 joints will be assessed for tenderness and swelling: metacarpophalangeal IV(10), thumb interphalangeal (2), hand proximal interphalangeal II-V (8), wrist (2), elbow(2), shoulders (2), and knees (2).

The following formulas can be used to calculate the DAS28 with CRP (mg/L) or ESR (mm/hour).

$$\text{DAS28-CRP} = 0.56*\text{sqrt}(\text{TJC28}) + 0.28*\text{sqrt}(\text{SJC28}) + 0.36*\ln(\text{CRP}+1) + 0.014*\text{PGA} + 0.96$$

$$\text{DAS28-ESR} = 0.56*\text{sqrt}(\text{tender28}) + 0.28*\text{sqrt}(\text{swollen28}) + 0.70*\ln(\text{ESR}) + 0.014*\text{PGA}$$

*TJC28: 28 Tender joint count; SJC28: 28 Swollen joint count; CRP: C-reactive protein; PGA: Patient Global Assessment*

If any component measurement is missing, DAS28 will be missing.

DAS28-CRP will be primary for analysis; DAS-ESR will be secondary.

DAS28-CRP (or ESR) remission is defined as a DAS28-CRP (or ESR) index score less than 2.6. Low disease activity is defined as DAS28-CRP (or ESR) index less than or equal to 3.2.

### **EULAR response**

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

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

**Table 11-1 EULAR response criteria**

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

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

### **Minimal disease activity**

A subject will be considered a responder of minimal disease activity (MDA, see [Coates 2010](#)) if he/she achieves at least 5 of the following 7 items:

- $\leq 1$  tender joint count
- $\leq 1$  swollen joint count
- PASI  $\leq 1$  or IGA  $\leq 1$
- patient pain VAS  $\leq 15$
- patient global VAS  $\leq 20$
- HAQ-DI  $\leq 0.5$
- tender enthesal points  $\leq 1$

## **ACR Components**

### ***Tender 78 joint count and swollen 76 joint count***

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

If the number of joints for which data were available (e.g., T) is less than 78/76 for the tender/swollen joint assessment, the number of tender/swollen joints (e.g., t) will be scaled up proportionately (i.e.,  $78*t/T$  or  $76*t/T$  for tender or swollen joint count).

### ***Patient's assessment of PsA Pain***

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*".

### ***Patient's global assessment of PsA 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*".

### ***Physician's global assessment of PsA 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 patient.

### ***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.

### ***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.

## **Magnetic Resonance Imaging**

Magnetic Resonance Imaging (MRI) will be performed in a subgroup of subjects with at least one swollen wrist at baseline at selected sites. The independent reviewers shall perform MRI assessments according to the modified PsAMRIS scoring method (Ostergaard, Mikkelsen et al 2009). Assessments will be performed on the hand with the more swollen wrist determined at baseline by the investigator. If both wrists are equally affected, the dominant hand/wrist will be chosen. The MRIs will be scored for the following assessments:

- Synovitis
- Tenosynovitis
- Periarticular inflammation
- Bone edema/osteitis
- Bone erosion
- Bone proliferation
- Joint space narrowing

Synovitis is defined as an area in the synovial compartment that shows greater than normal postgadolinium enhancement of a thickness greater than the estimated width of the normal synovium. A total of 17 locations in the hand and wrist will be evaluated for synovitis. Synovitis will be assessed on a scale of 0-3 for each location. The maximum possible score for synovitis is 51.

Tenosynovitis is defined as an area with signal characteristics that show greater than normal water content or greater than normal post-gadolinium enhancement adjacent to a tendon, in an area with tendon sheath. A total of 14 hand locations and 10 wrist regions will be evaluated for tenosynovitis. Synovitis will be assessed on a scale of 0-3 for each location. The maximum possible score for tenosynovitis in the hand and wrist is 72.

Periarticular inflammation is defined as an area with signal characteristics that show greater than normal water content or greater than normal post-gadolinium enhancement at extraarticular sites including the periosteum and the entheses (not including tendon sheaths as this is defined as tenosynovitis). A total of 28 locations in the hand will be evaluated for periarticular inflammation. Periarticular inflammation will be assessed on a scale of 0-2 for each location. The maximum possible score for periarticular inflammation in the hand is 56.

MRI edema/osteitis is defined as a lesion, that may occur alone or surrounding an erosion or other bone abnormalities, within the trabecular bone, often with ill-defined margins and signal characteristics consistent with increased water. A total of 43 locations will be evaluated for bone edema/osteitis. Bone edema/osteitis is scored on a scale of 0-3 based on the proportion of estimated originally noneroded bone involved. The maximum possible score for bone edema/osteitis is 129.

MRI bone erosion is defined as a sharply marginated bone lesion, with correct juxta-articular localization and typical signal characteristics, with a cortical break seen in at least one plane. A total of 43 locations will be evaluated for bone erosions. Each bone is scored on a scale of 0-10. The maximum possible score for bone erosions is 430.

Bone proliferation is defined as an abnormal bone formation in the periarticular region such as at the entheses and across the joint. A total of 14 joints will be evaluated for bone proliferation. Bone proliferation will be assessed on a scale of 0-2 for each location. The maximum possible score for Bone proliferation is 28.

Joint space narrowing (JSN) is defined as the reduction in joint space. JSN is scored on a scale of 0-4 based on the amount of narrowing present in a given joint. The maximum possible score for JSN in all 29 hand joints is 116.

If a joint or bone is not visible (e.g. poor image quality, missing imaging, severe misalignment, flexion deformity, dislocation, ankylosis of >50% of articular surface [for erosion score only]) at the timepoint, the individual joint or bone will be coded as Not Visible (N). If MRIs at the timepoint show a joint or bone with surgical fusion, replacement (prosthesis), or amputation, then the joint or bone will be scored Surgically Modified (S). To obtain the total score per feature, any "N" or "S" will be considered null in the calculation.

The score per feature will be calculated as the sum of scores from all available locations per feature.

### **PsARC response**

A subject is defined as a PsARC responder if, and only if, they have an improvement in two of the following four factors (with at least one factor being a joint count) and no worsening in the remaining factors

- Patient global assessment (0-100 mm VAS scale, improvement defined as decrease of at least 20 mm)
- Physician global assessment (0-100 mm VAS scale, improvement defined as decrease of at least 20 mm)
- Tender 78-joint count (improvement defined as decrease of at least 30%)
- Swollen 76-joint count (improvement defined as decrease of at least 30%)

PsARC response won't be calculated if any of the four components are missing.

### **Leeds Enthesitis Index (LEI)**

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. Tenderness on examination is recorded as either present (1) or absent (0) for each of the 6 sites, for an overall score range of 0–6. Higher count represents greater enthesitis burden.

In this study, the lateral condyle femur L + R data were collected instead of required medial condyle femur L + R. Therefore, a 4-site LEI (LEI-4) will be calculated with the four correct sites: lateral epicondyle humerus L + R, proximal achilles L + R. If measures are missing for any of these four sites, the LEI-4 won't be calculated.

### **Presence of enthesitis**

If enthesitis is present with any of the 4 sites (lateral epicondyle humerus L + R, proximal achilles L + R), the patient is counted as a patient with enthesitis.

### **Leeds Dactylitis Index (LDI)**

The LDI measures the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot: a minimum difference of 10% is used to define a dactylitic digit. If both sides are considered involved, a table of normative values is used to provide the comparison. The ratio of circumference is multiplied by a tenderness score, originally based on the Ritchie index (graded 0–3), but a later modification amended this to a binary score (0 for nontender, 1 for tender) — this later modification is referred to as the LDI basic, and is adopted in this study. For each dactylitic digit, the final score is:

$$[\{(A/B) - 1\} * 100] * C,$$

where A is circumference of involved digit, B circumference of opposite (unaffected or from reference) and C is tenderness (0 or 1 in this case). The results from each digit with dactylitis are then summed to produce a final score. Only involved digits are assessed.

### **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 patient is counted as a patient with dactylitis.

### **Psoriasis Area and Severity Index (PASI)**

The PASI assessment will be conducted for subjects in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at baseline (Visit 2). 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 will be derived as indicated in [Table 11-2](#). 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:

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

**Table 11-2 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	0=none	0=none	0 = 0%
	1=slight	1=slight	1=slight	1 = 1-9%
	2=moderate	2=moderate	2=moderate	2 = 10-29%
	3=severe	3=severe	3=severe	3 = 30-49%
	4=very severe	4=very severe	4=very severe	4 = 50-69%
				5 = 70-89% 6 = 90-100%
Trunk, (T)***	0=none	0=none	0=none	0 = 0%
	1=slight	1=slight	1=slight	1 = 1-9%
	2=moderate	2=moderate	2=moderate	2 = 10-29%
	3=severe	3=severe	3=severe	3 = 30-49%
	4=very severe	4=very severe	4=very severe	4 = 50-69%
				5 = 70-89% 6 = 90-100%
Upper limbs (U)	0=none	0=none	0=none	0 = 0%
	1=slight	1=slight	1=slight	1 = 1-9%
	2=moderate	2=moderate	2=moderate	2 = 10-29%
	3=severe	3=severe	3=severe	3 = 30-49%
	4=very severe	4=very severe	4=very severe	4 = 50-69%
				5 = 70-89% 6 = 90-100%
Lower limbs (L)****	0=none	0=none	0=none	0 = 0%
	1=slight	1=slight	1=slight	1 = 1-9%
	2=moderate	2=moderate	2=moderate	2 = 10-29%
	3=severe	3=severe	3=severe	3 = 30-49%
	4=very severe	4=very severe	4=very severe	4 = 50-69%
				5 = 70-89% 6 = 90-100%

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

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

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

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

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

$$\text{PASI} = 0.1(\text{E}_H + \text{I}_H + \text{D}_H)\text{A}_H + 0.2(\text{E}_U + \text{I}_U + \text{D}_U)\text{A}_U + 0.3(\text{E}_T + \text{I}_T + \text{D}_T)\text{A}_T + 0.4(\text{E}_L + \text{I}_L + \text{D}_L)\text{A}_L$$

The keys for the letters are provided in [Table 11-2](#).

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 total score comes from eCRF.

### IGA mod 2011

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

The IGA mod 2011 rating scale for overall psoriatic disease is displayed in [Table 11-3](#).

**Table 11-3 The IGA mod 2011 rating scale**

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

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

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

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

Based on this scale, subjects will be considered as **IGA mod 2011 0 or 1 responder** if they achieve a score of 0 or 1 and improve by at least 2 points on the IGA scale compared to baseline.

### Target lesion score (TLS)

The Target Lesion Score will be done for subjects enrolled in the study having a psoriatic target lesion that is at least 2 cm in diameter identified at baseline. At specified visits this target lesion will be scored for erythema, scaling, and thickness, each on a scale of 0 to 4 (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe). The parameter scores will be summed automatically in the eCRF, giving a score ranging from 0 to 12.



## 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. The mNAPSI scores range from 0-130 for all finger nails. The total mNAPSI score will be calculated as the sum of all the scores from available nails.

## 11.2 Description of Health-related Quality of Life Endpoints

### SF-36

The Short Form Health Survey (SF-36) is a widely used and extensively studied instrument to measure health-related quality of life among healthy subjects and patients 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 patients.

### FACIT - Fatigue

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue<sup>®</sup>) is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function.

Subjects respond to each item on a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much) based on their experience of fatigue during the past 2 weeks. The scale score is computed by summing the item scores, after reversing those items that are worded in the negative direction. Numbering the questions from 1 to 13, it is evident that questions 7 and 8 are worded in the positive direction (4 indicates a desirable response) and all other questions are worded in the negative directions (4 indicates an undesirable response). Thus, it is necessary to reverse the responses for questions 7 and 8 (i.e. original response of 0 gets mapped to 4, 1=3, 2=2, 3=1, and 4=0) for scoring purposes.

When there are missing item scores, the subscale score was computed by summing the non-missing item scores, multiplying by 13 (the total number of items in the scale) and dividing by the number of non-missing items (i.e. normalizing the results). The latter rule applied only when at least half of the items (seven or more) are non-missing.

FACT Fatigue subscale scores range from 0 to 52, where higher scores represent less fatigue (Cella D et al., 2004).

### **EuroQoL 5D (EQ-5D)**

The EQ-5D is a widely used, self-administered questionnaire designed to assess health status in adults. The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Subjects rate each of these items from "no problem," "some problem," or "extreme problem." A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is "today," and the questionnaire requires approximately 5 to 10 minutes to complete.

The EQ-5D contains six items designed to assess health status in terms of a single index value or health utility score. One of the strengths of the EQ-5D approach is that it allows "weighting" by the patient of particular health states and the generation of patient utilities. Published weights are available that allow for the creation of a single summary health utility score. Overall scores range from 0 to 1, with lower scores representing a higher level of dysfunction.

### **PsAQoL**

The PsA quality of life (PsAQoL) questionnaire contains 20 individual yes/no questions where the total score is determined by the number of questions that received a "yes" response. A higher score reflects a poorer quality of life.

The PsAQoL score will not be calculated if more than 4 questions are missing. Otherwise, divide the number of 'yes' by the number of answered questions, multiply by 20.

### **Dermatology Life Quality Index (DLQI)**

The Dermatology Life Quality Index (DLQI) is a 10-item general dermatology disability index designed to assess health-related quality of life in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral warts. The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 32 different skin conditions and is available in multiple languages. The recall period is the past week, and the instrument requires 1 to 2 minutes for completion.

Each item has four response categories ranging from 0 (not at all) to 3 (very much). "Not relevant" is also a valid response and is scored as 0. The DLQI total score is a sum of the 10 questions. Scores range from 0 to 30, and higher scores indicate greater health-related quality of life impairment. If two or more questions are left unanswered, the total score will not be calculated.

### **Work Productivity and Activity Impairment - General Health (WPAI-GH)**

The Work Productivity and Activity Impairment (WPAI-GH) questionnaire is an instrument to measure impairments in both paid work and unpaid work. It measures absenteeism,

presenteeism as well as the impairments in unpaid activity because of health problem during the past seven days. The WPAI-GH consists of six questions:

- 1 = currently employed
- 2 = hours missed due to health problems
- 3 = hours missed other reasons
- 4 = hours actually worked
- 5 = degree health affected productivity while working (VAS)
- 6 = degree health affected productivity in regular unpaid activities (VAS)

The recall period for the questions 2 to 6 is seven days.

Four main outcomes can be generated from the WPAI-GH and expressed in percentages by multiplying the following scores by 100:

- 1) percent work time missed due to health =  $Q2/(Q2 + Q4)$  for those who were currently employed;
- 2) percent impairment while working due to health =  $Q5/10$  for those who were currently employed and actually worked in the past seven days;
- 3) percent overall work impairment due to health  $Q2/(Q2 + Q4) + ((1 - Q2/(Q2 + Q4)) \times (Q5/10))$  for those who were currently employed;
- 4) percent activity impairment due to health  $Q6/10$  for all respondents.

For those who missed work and did not actually work in the past seven days, the percent overall work impairment due to health will be equal to the percent work time missed due to health.

### **11.3 Handling of missing data**

#### **Missing data**

Missing data for ACR20 response and other binary efficacy variables for data up to 1-year (Week 52) will be handled as follows:

- 1. Subjects who drop out of the trial for any reason will be considered non-responders from the time they drop out through Week 52.
- 2. Subjects who do not have the required data to compute ACR20 response at baseline and at the specific time point will be classified as non-responders.

Patients who were unblinded prior to the scheduled timepoint will be considered non-responders from the time of unblinding up to the end of the placebo-controlled period (Week 24). The primary analysis will use the non-responder imputation.

Continuous variables (e.g. ACR20 components) will be analyzed using a mixed-effects repeated measures model (MMRM) which is valid under the missing at random (MAR) assumption. As such, single-point imputation of missing data will not be performed (e.g. LOCF). For analyses of these parameters, if all post-baseline 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.

### **Data post-rescue**

In general, the handling of data for subjects who are rescued at Week 16 will be handled in the following fashion (up to Week 24):

- For binary endpoints, subjects will be considered non-responders. This will be done for all treatment regimens in order to minimize bias.
- For continuous endpoints, the goal of the analyses would be to estimate what would have happened if the patients had stayed on the original treatment. Thus, the data collected after the patient switches to secukinumab will be treated as missing for placebo patients and will be analyzed using a mixed-effects repeated measures model (MMRM) which is valid under the missing at random (MAR) assumption. For secukinumab patients, the actual values will be used in the analysis.

Data collected after Week 52 will generally be presented as ‘observed case’; i.e. all available data for each time point will be included in the analyses.

## **11.4 Analysis of Primary variable**

The primary efficacy variable will be ACR20 response at Week 24. The analysis of the primary efficacy variable will be based on the FAS. Primarily, CRP will be used instead of ESR to calculate ACR response; ESR will only be used in the event CRP is missing.

### **Statistical analysis**

The statistical hypothesis for ACR20 being tested is that there is no difference in the proportion of subjects fulfilling the ACR20 criteria at Week 24 in any of the secukinumab regimens versus placebo regimen.

Let  $p_j$  denote the proportion of ACR20 responders at Week 24 for treatment regimens  $j, j=0, 1, 2$ , where

- 0 corresponds to placebo regimen,
- 1 corresponds to secukinumab 75 mg s.c.,
- 2 corresponds to secukinumab 150 mg s.c.,

In statistical terms,  $H_j: p_j = p_0$ ,  $H_{A_j}: p_j \neq p_0$ , for the  $j^{\text{th}}$  secukinumab regimen, i.e.

$H_1$ : secukinumab 75 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24

$H_2$ : secukinumab 150 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24

The primary endpoint of ACR20 at Week 24 will be analyzed via logistic regression with treatment and TNF-alpha inhibitor status as factors and weight as a covariate. Odds ratios will be computed for comparisons of secukinumab regimens versus placebo regimen utilizing the logistic regression model fitted.

For subjects meeting the criteria for early escape at Week 16, their ACR20 will be set to non-response at Week 24. This applies for all three treatment regimens in order to minimize bias.

### **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.

In order to determine the robustness of the logistic regression model used for the primary analysis, ACR20 response at Week 24 will also be evaluated using a non-parametric regression ([Koch et. al 1998](#)) model with the same independent variables as the logistic regression model. In addition, further logistic regression models may be conducted which explore the impact of other baseline or disease characteristics on response. Treatment by factor interactions will be explored.

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:

- Multiple imputation
- Observed data analysis

### **11.5 Analysis of secondary variables**

The secondary efficacy variables include:

- response to treatment at Week 24 according to the PASI75 criteria in the subgroup of subjects who have  $\geq 3\%$  skin involvement
- response to treatment at Week 24 according to the PASI90 criteria in the subgroup of subjects who have  $\geq 3\%$  skin involvement
- change from baseline in DAS28-CRP at Week 24 in the FAS
- change in SF-36 PCS from baseline at Week 24 in the FAS
- change in HAQ-DI from baseline at Week 24 in the FAS
- response to treatment at Week 24 according to the ACR50 criteria in the FAS
- change from baseline in mTSS at Week 24 pooled secukinumab regimen vs placebo in the FAS
- presence of dactylitis at Week 24 pooled secukinumab regimen vs placebo in the subset of subjects who have dactylitis at baseline
- presence of enthesitis at Week 24 pooled secukinumab regimen vs placebo in the subset of subjects who have enthesitis at baseline
- change from baseline in mTSS at Week 24 individual secukinumab regimen vs placebo in the FAS

### **Testing strategy to control type I error**

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:

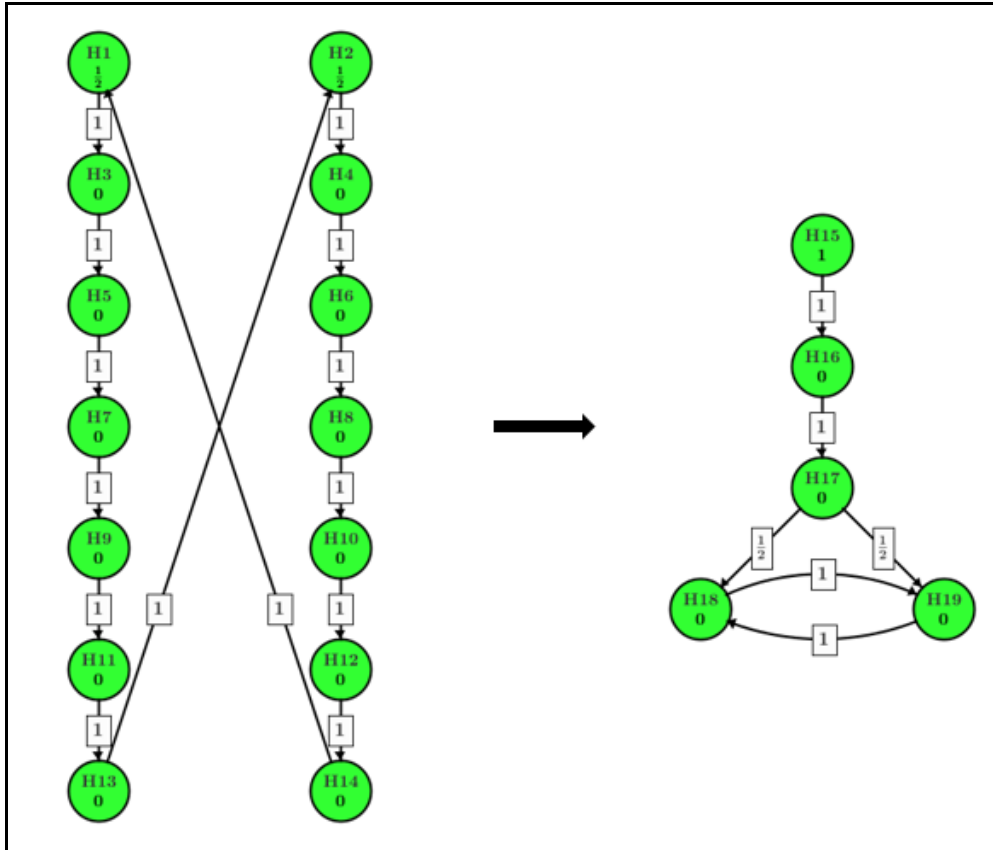
- H<sub>1</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to ACR20 response at Week 24
- H<sub>2</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to ACR20 response at Week 24

Secondary objectives:

- H<sub>3</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to PASI75 response at Week 24
- H<sub>4</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to PASI75 response at Week 24
- H<sub>5</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to PASI90 response at Week 24
- H<sub>6</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to PASI90 response at Week 24
- H<sub>7</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for DAS28-CRP at Week 24
- H<sub>8</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for DAS28-CRP at Week 24
- H<sub>9</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for SF36-PCS at Week 24
- H<sub>10</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for SF36-PCS at Week 24
- H<sub>11</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at Week 24
- H<sub>12</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at Week 24
- H<sub>13</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to ACR50 response at Week 24
- H<sub>14</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to ACR50 response at Week 24
- H<sub>15</sub>: Secukinumab pooled regimen (75 mg and 150 mg s.c.) is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24
- H<sub>16</sub>: Secukinumab pooled regimen (75 mg and 150 mg s.c.) is not different to placebo regimen with respect to presence of dactylitis at Week 24
- H<sub>17</sub>: Secukinumab pooled regimen (75 mg and 150 mg s.c.) is not different to placebo regimen with respect to presence of enthesitis at Week 24
- H<sub>18</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24
- H<sub>19</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24

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

**Figure 11-1 Testing strategy**



The family-wise error will be set to  $\alpha=5\%$  and it will be controlled with the proposed hierarchical testing strategy. With this hierarchical testing approach, the hypotheses will be separated into two families, hypotheses of signs and symptoms ( $H_1 \sim H_{14}$ ) will be the first family and hypotheses of structure damage ( $H_{15} \sim H_{19}$ ) will be the second family. The second family hypotheses will be tested only when all hypotheses in the first family have been rejected. Each of the hypotheses ( $H_1$  and  $H_2$ ) for the primary objective (based on signs and symptoms at week 24) for each secukinumab regimen versus placebo will be tested simultaneously at  $\alpha/2$ . If at least one of  $H_1$  and/or  $H_2$  are/is rejected, then  $H_3$  and/or  $H_4$ , respectively. If at least one of  $H_3$  and/or  $H_4$  is rejected, the hypothesis  $H_5$  and/or  $H_6$ , is tested, respectively. Similar process applies until  $H_{13}$  and  $H_{14}$ . Once all hypotheses within the first family for a secukinumab regimen are rejected, then the respective  $\alpha/2$  can be passed on to the other regimen's hypotheses within the family, if they are not already rejected at  $\alpha/2$ . Only when all  $H_1 \sim H_{14}$  are rejected, the objective on joint structure endpoint at Week 24 for testing pooled secukinumab doses versus placebo ( $H_{15}$ ) will be tested at  $\alpha$ . If  $H_{15}$  is rejected, then  $H_{16}$  is tested at  $\alpha$ . Similarly if  $H_{16}$  is rejected, then  $H_{17}$  is tested at  $\alpha$ . If these pooled hypotheses are all rejected, then hypotheses concerning individual regimens of secukinumab versus placebo ( $H_{18}$  and  $H_{19}$ ) can be tested for a particular regimen at  $\alpha/2$ . Once the hypothesis of structure

damage for a secukinumab regimen is rejected, then the respective  $\alpha/2$  can be passed on to the other regimen's hypothesis, if it is not already rejected at  $\alpha/2$ . Of note, in the description above, rejection of a hypothesis refers to rejection of the two-sided hypothesis; however the level of a rejected hypothesis is only passed on according to the graphical procedure for the test of another hypothesis if the treatment effect is in favor of secukinumab.

### **PASI 75 and PASI 90 response**

PASI 75 response and PASI 90 at Week 24 will be evaluated for those subjects in whom the assessment occurred (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.

### **Changes in DAS28-CRP**

Between-treatment differences in the change from baseline in DAS28-CRP will be compared by means of a mixed model repeated measures (MMRM) with treatment regimen, analysis visit, and TNF-alpha inhibitor status as factors, and weight and baseline as continuous covariates. Treatment by analysis visit and baseline 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 secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

### **SF-36 PCS**

Between-treatment differences in the change in SF-36 PCS will be evaluated using a mixed effect repeated measures model (MMRM). Treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline SF-36 score and weight as continuous covariates. Treatment by analysis visit and baseline 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.

### **Physical function (HAQ-DI)**

Between-treatment differences in the change in HAQ-DI 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 baseline HAQ-DI score as continuous covariates. Treatment by analysis visit and baseline 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 secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.



### **ACR50 at Week 24**

Response at Week 24 to ACR50 in the FAS will be evaluated using a logistic regression model with treatment and randomization stratum (TNF $\alpha$  status -naive or IR) as factors and weight as a covariate.

### **Joint/bone structural damage at Week 24**

The change at Week 24 from baseline van der Heijde total modified Sharp score will be evaluated using a non-parametric ANCOVA model with treatment regimen and TNF-alpha inhibitor status as factors, and weight and baseline van der Heijde total modified Sharp score as covariates. The pooled secukinumab regimens (75 mg s.c. and 150 mg s.c.) will be compared to placebo, then each of the secukinumab regimens will be compared versus the placebo regimen via pairwise comparisons.

For subjects who meet the criteria for early escape at Week 16 and subjects who discontinue the study prior to Week 24, linear extrapolation will be used to impute the value at Week 24. In order to minimize bias, the extrapolation will use baseline and all post-baseline data up to the point the subject meets criteria for early escape treatment, or discontinues the study. If baseline or all post-baseline total modified Sharp score/s is/are missing for a subject, the subject will be excluded from the analyses.

### **Dactylitis at Week 24**

Presence of dactylitis at Week 24 in the subset of subjects who have dactylitis at baseline will be evaluated using a logistic regression model with treatment and randomization stratum (TNF $\alpha$  status -naive or IR) as factors and weight as a covariate.

### **Enthesitis at Week 24**

Presence of enthesitis at Week 24 in the subset of subjects who have enthesitis at baseline will be evaluated using a logistic regression model with treatment and randomization stratum (TNF $\alpha$  status -naive or IR) as factors and weight as a covariate.

## **11.6 Analysis of exploratory variables**

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

- HAQ response
- Major clinical response by Week 52 and 104
- Joint/bone structural damage at Week 52 and 104
- Evidence of no disease progression at Week 24, 52 and 104
- PsARC, ACR20/50/70 response over time
- DAS28 remission, low disease activity, EULAR response at Week 24 and over time
- Minimal disease activity
- ACR components
  - Changes in tender joint counts over time
  - Change in swollen joint counts over time
  - Change in Patient's global assessment in disease activity
  - Change in Physician's global assessment in disease activity

- Change in PsA Pain
- Change in HAQ-DI over time
- Change in erythrocyte sedimentation rate (ESR)
- Change in high-sensitivity C-reactive protein (hsCRP)
- PASI 75, PASI 90, and IGA response over time
- Target lesion score
- mNAPSI
- LDI and dactylitis count
- LEI-4

Between-treatment comparisons for binary variables in the FAS population (e.g. PsARC, ACR20, etc.) at individual analysis visits will be evaluated using a logistic regression model with treatment and TNF-alpha inhibitor status as factors and baseline score (if appropriate) and weight as covariates.

Continuous variables (e.g. change from baseline in PsA pain) will be evaluated using a mixed-effect model repeated measures (MMRM) with treatment regimen, TNF-alpha inhibitor status, and analysis visit as factors and weight and baseline score as continuous covariates. Treatment by analysis visit and baseline 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 secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits. Variables such as hsCRP whose distribution is not anticipated to be normal will be transformed and analyzed on the log<sub>e</sub> scale.

### **Joint/bone structural damage at Week 52 and 104**

Observed joint/bone structure data at Week 52 will be compared between subjects randomized at baseline to secukinumab regimen (pooled from 2 secukinumab regimens) and placebo followed by secukinumab regimen. The change from baseline to Week 52 will be evaluated using a non-parametric ANCOVA model utilized for Week 24 and including randomization strata as a covariate.

As sensitivity analysis, for subjects with missing modified Sharp score values at Week 52, their Week 52 value will be imputed by linear extrapolation from baseline, Week 16 and Week 24, and at subject discontinuation visit (if subject discontinued prior to Week 52) to Week 52.

Summary statistics of observed data at Week 52 will be provided for each treatment regimens: secukinumab 75 mg, secukinumab 150 mg, placebo escape or switch to secukinumab 75 mg at Week 16 or 24, placebo escape or switch to secukinumab 150 mg at Week 16 or 24. Summary statistics include mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum.

Observed Joint/bone structure data at Week 104 will be summarized by treatment group. In addition, the change from week 52 will also be summarized within treatment regimen.

### **Evidence of no disease progression at Week 24, 52 and 104**

The proportion of subjects without disease progression will be defined as those subjects who have a change in van der Heijde total modified Sharp score at Week 24 relative to baseline  $\leq 0$ . The proportion of subjects without disease progression at Week 24 will be evaluated using a logistic regression model with treatment group and randomization strata, as factors, weight and baseline van der Heijde total modified Sharp score as covariates.

The proportion of subjects without disease progression at Week 52 and 104 will be evaluated in the same manner. At week 104, the proportion of subjects with disease progression from week 52 will also be examined.

### **EULAR response at Week 24 and over time**

Based on the EULAR response criteria (good responder, moderate responder, and non-responder) as determined based on the value of DAS28-CRP achieved and the magnitude of change from baseline, between-treatment differences in EULAR response at Week 24 and other analysis visits will be evaluated using a proportional odds regression model with treatment group and randomization strata as factors and weight and baseline DAS28-CRP score as covariates. Frequency tables will also be presented to show the response rate over time up to Week 24 and Week 52, as appropriate.

### **Magnetic Resonance Imaging**

MRI Analysis will be based on the patients who have MRI performed at selected centers.

The change in synovitis between Week 24 and baseline will be evaluated using a nonparametric ANCOVA model with treatment regimen as a factor, weight and baseline erosion score as covariates. Pair-wise comparison versus placebo will be made for each of the secukinumab regimens. Tenosynovitis, periarticular inflammation, bone edema/osteitis, bone erosion, bone proliferation, and joint space narrowing will be evaluated in the same manner.

For subjects with missing data at Week 24, linear extrapolation will be used to impute missing data. In order to minimize bias, the extrapolation will use baseline and week 12. Change from baseline will be summarized by analysis visit with summary statistics including mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum.

#### **LEI-4**

The 4-site LEI (i.e. score with the four correct sites: lateral epicondyle humerus L + R and proximal achilles L + R) will be summarized by treatment group and visit. Change from baseline in the 4-site LEI will be analyzed using a nonparametric ANCOVA model with treatment regimen and randomization strata as factors, weight and baseline score as covariates. Pair-wise comparison versus placebo will be made for each of the secukinumab regimens by visit.

## 11.7 Analysis of Health-related Quality of life variables

### PsAQoL

Between-treatment differences in the change from baseline for PsAQoL scores will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline and weight as continuous covariates. Treatment by analysis visit and baseline 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.

### SF-36

The following variables will be evaluated:

- SF-36 domain scores.
- SF-36 PCS and MCS scores.
- SF-36 PCS responder (improvement of  $\geq 2.5$  points, [Lubeck 2004](#))

Between-treatment differences in the change from baseline for SF-36 summary scores (PCS/MCS) will be evaluated using a mixed effect repeated measures model (MMRM). Treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline SF-36 score and weight as continuous covariates. Treatment by analysis visit and baseline 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.

In the responder analyses, treatment groups will be compared with respect to response to treatment using a logistic regression model with treatment and TNF-alpha inhibitor status as factors, baseline SF-36 summary score and weight as covariates. Odds ratios with corresponding 95% confidence intervals will be estimated in addition.

Individual SF-36 domain scores will be summarized.

### FACIT-Fatigue

Between-treatment differences in the change from baseline for FACIT-Fatigue scores will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline and weight as continuous covariates. Treatment by analysis visit and baseline 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.

### **EuroQol 5D (EQ-5D)**

The number and percentage of subjects in each of the three categories for each question will be presented by visit and treatment group.

Summary statistics will be shown for the health state assessment by visit and treatment group.

For the change in EQ-5D overall health state (VAS), between-treatment differences in the change in EQ-5D overall health state (VAS) will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline EQ-5D overall health state (VAS) and weight as continuous covariates. Treatment by analysis visit and baseline EQ-5D overall health state (VAS) 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.

### **Dermatology Life Quality Index (DLQI)**

Between-treatment differences in the change from baseline for DLQI will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline and weight as continuous covariates. Treatment by analysis visit and baseline 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.

### **WPAI-GH**

Summary statistics will be shown for the WPAI-GH assessment by visit and treatment group.

## **12 Pharmacokinetic evaluations (change / add PD, PK/PD, Biomarkers, as needed)**

### **12.1 Pharmacokinetics**

All completed subjects with quantifiable pharmacokinetic (PK) measurements of secukinumab will be included in the pharmacokinetic data analysis. Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification as well as missing data will be labeled as such in the concentration data listings. PK concentrations will be summarized by visit and treatment group. In addition to mean, standard deviation (SD), coefficient of variation (CV), median and quartiles, the geometric mean and geometric coefficient of variation (CV) and n(log) will be presented. The formula for deriving the geometric mean and CV (%) is as following:

- $CV (\%) = (SD/mean)*100,$

- geometric mean= $\exp(\text{sum of log transformed data} / \text{number of non-missing data points after log transformation})$ ,
- geometric CV =  $\sqrt{\exp(\text{variance of log-transformed data}) - 1} * 100$ .

In addition, sample number, concentration, sample date, sample time at pre-dose and minutes pre-dose will be listed by treatment sequence.

Values below lower limit of quantification/below detection limit will be imputed by 0.

Pharmacokinetic data of the study treatment will be analyzed with a population-pharmacokinetic mixed effects model. The analysis will be based on a pooled data set, including pharmacokinetic samples from previous studies. The modeling approach will be further detailed in a modeling plan. Results will be reported separately.

## **12.2 Pharmacogenetics**

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations will be evaluated with exploratory analyses. A range of statistical tests (chi-square tests, analysis of covariance (ANCOVA), linear and logistic regression) will be used for the analyses. Additional data, from subsequent clinical trials, are often needed to confirm associations. Alternatively, if the numbers of subjects enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

Results will be reported separately.

## **12.3 Biomarkers**

Soluble marker panel studies investigate differences in the level of expression of proteins or peptides between individuals in a given biofluid. The goal of such studies is to allow the identification of potential protein or peptide biomarkers of drug action or disease, and to better understand the associated underlying molecular mechanisms. By applying statistical analysis methods (e.g. principal component analysis) between subject groups, distinct study time points, or between study groups from other clinical trials, it may be possible to identify patterns which are associated with disease state or response to drug treatment. However, the exact type of data analysis method will depend on the type of data obtained in the study and thus the analysis of this data will be data driven.

Results will be reported separately.

## **12.4 PK/PD**

Exploratory analysis to investigate the correlation between the PK data and efficacy outcomes will be performed.

An indirect response model, driven by study treatment concentration, will be used to characterize the time course of efficacy response. Further details of the modeling approach will be specified in a modeling plan. Results will be reported separately.

## 13 Safety evaluation

Summaries may be performed separately for initial (Week 1-16) and entire treatment periods. Week 16 is chosen due to the fact that placebo patients may be rescued as early as week 16. Use of data up to and including the last visit before rescue provides an unbiased comparison between AIN and placebo; data collected beyond week 16 are included in analyses which summarize the entire treatment period. The analyses of the follow-up period will be limited to summaries for treatment-emergent adverse events, serious adverse events and risks based on adverse events.

Safety analyses will be performed on treatment received or actual treatment as described below:

The actual treatment or treatment received for summaries of safety data will differ to the treatment assigned at randomization only if a subject received the wrong treatment during the entire study.

For those subjects who received not the treatment randomized, i.e. who received erroneously the wrong treatment at least once, an additional AE listing will be prepared displaying which events occurred after the treatment errors.

### 13.1 Adverse events

The crude incidence of treatment emergent adverse events (i.e. events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized by primary system organ class and preferred term. Confidence intervals for the crude rate will be derived as described in [Section 18.2.4.1](#). In addition, exposure time-adjusted rates (incidence rate as well as event rate) including 95% confidence intervals will be provided for the entire treatment period (see [Section 18.2.5.1](#)) to adjust for differences in exposure. A graphical display of the crude incidence rates and exposure-adjusted rates within system organ classes will be presented for all AEs and serious AEs.

The most common adverse events reported ( $\geq 1\%$  in any group for each preferred term in the SOC-PT table or  $\geq 1\%$  in any group for each SMQ table) will be presented in descending frequency according to its incidence in total secukinumab group (combining all secukinumab treatment groups) starting from the most common event. Summaries (crude incidences only) will also be presented for AEs by severity and for study treatment related AEs. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event 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.

A graphical display of the crude rates or exposure adjusted incidence rates within system organ classes will be presented as follows: For all AEs regardless of severity and seriousness, the point estimate (i.e. relative frequency for evaluation of initial treatment and exposure adjusted incidence for evaluation of entire treatment) within system organ classes will be presented graphically with system organ class on the y-axis. This figure will consist of two

panels: i) point estimate of AEs, ii) point estimate of serious AEs. The placebo group will be displayed with a bar whereas dots will be used for secukinumab treatment groups. For the exposure adjusted incidences a linear scale will be used on the x-axes.

Additional plots will be provided showing point estimates and confidence intervals on the left panel and numeric values of point estimate and confidence interval on the right panel of the figure. This will be done separately for all AEs and all SAEs.

Separate summaries will be provided for adverse events suspected to be related to study drug, deaths, serious adverse events, and adverse events leading to discontinuation and adverse events leading to dose adjustment.

Adverse events will also be reported separately by SMQ according to MedDRA, using a narrow search. The MedDRA version used for reporting the study will be described in a footnote.

Follow-up period summaries will be done for all subjects in follow-up who do not go on to the extension study (completers and early discontinuations).

A listing of non-treatment emergent adverse events will be done. These adverse events occurred before the first dose of the study treatment. The crude incidence rate will be provided without treatment information.

Algorithms for date imputations will be provided in RAP M8.

For SAEs occurred during screening a listing will be prepared for all subjects screened including screening failures.

An overview of the safety analyses and which will be performed for each analysis period is described in [Table 13-1](#).

**Table 13-1 Overview of analyses on some safety endpoints**

Analysis period	AEs & SAEs	AEs by severity	Study drug related AEs	AEs-SMQ	Risk	Notables for (vitals/ ECG), lab criteria
Day 1 – Week 16	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence
Day 1 – Week 24	• exposure time adjusted incidence*					
Entire Treatment (up to week 104)	• crude incidence • exposure time adjusted incidence*	• crude incidence	• crude incidence	• exposure time adjusted incidence	• crude incidence • exposure time adjusted incidence	• crude incidence
follow-up (week 104 to 112)	• crude incidence				• crude incidence	

\*Exposure-adjusted incidence rates will be done at the PSOC for AE and SAE and Level 1 for Risks and SMQ analyses



## 13.2 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, chemistry and urinalysis). In addition to the individual laboratory parameters the ratios “total cholesterol / HDL” and “apolipoprotein B / apolipoprotein A1” will be derived and summarized.

For urinalysis, frequency tables will be presented.

Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values and will be calculated as:

$$\text{change from baseline} = \text{post baseline value} - \text{baseline value}$$

For each parameter, the maximum change (maximum decrease and maximum increase) from baseline, if appropriate for each study phase, will be analyzed analogously.

In addition, shift tables will be provided for all parameters to compare a subject’s baseline laboratory evaluation relative to the visit’s observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. If appropriate, the shifts to the most extreme laboratory test value within a treatment phase (either initial or entire) will be presented as well (including category “high and low”). These summaries will be presented by laboratory test and treatment group.

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in [Table 13-2](#): hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose, cholesterol, triglycerides (TG).

These summaries will be split into hematology and chemistry for study level reports and the pooled summary of clinical safety.

**Table 13-2 CTCAE grades for laboratory parameters to be analyzed**

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	
Platelet count decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased*	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
TBL increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Glucose increased (Hyperglycemia )	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Glucose decreased (Hypoglycemia)	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L
Cholesterol high	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
Hypertriglyceridemia	1.71 - 3.42 mmol/L	>3.42 - 5.7mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L

\*Note: for “creatinine increased” the baseline criteria do not apply

Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment phase (either initial or entire) analyzed. Of note, baseline will be defined as last assessment prior to first dosing in initial treatment phase. Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

Summaries for newly occurring or worsening clinically notable lipid abnormalities will also be provided cumulatively for each of the following parameters and categories:

- HDL:
  - $\leq$ LLN
  - $<0.8 \times$  LLN
- LDL, cholesterol, triglycerides:
  - $\geq$ ULN
  - $>1.5 \times$  ULN
  - $>2.5 \times$  ULN

Newly occurring or worsening liver enzyme abnormalities will also be summarized based on the event criteria given in [Table 13-3](#):

**Table 13-3 Liver-related events**

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
TBL	>1.5xULN, >2xULN, >3xULN,
ALP	>2xULN, >3xULN. >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >8xULN & TBL >2xULN; ALT or AST >10xULN & TBL >2xULN
ALP & TBL	ALP >3xULN & TBL >2xULN ALP >5xULN & TBL >2xULN
ALT or AST & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP <2xULN ( <b>Hy's Law</b> ) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of <i>pure hepatocellular injury</i> . This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP ≥2xULN may not result in severe DILI.

Notes:

1) In studies which enroll subjects with pre-existing liver disease, baseline LFT may be increased above ULN; in such a case it is meaningful to add the condition "and worse than baseline" to the abnormality criteria

For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same visit. The criteria are not mutually exclusive, e.g. a subject with ALT = 6.42xULN is counted for ALT >3xULN and ALT>5x ULN.

Individual subject data listings will be provided for subjects with abnormal laboratory data. Data of subjects with newly occurring or worsening liver enzyme abnormalities will be listed in an additional listing.

### 13.3 Vital signs

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

$$\text{change from baseline} = \text{post-baseline value} - \text{baseline value}$$

The number and percentage of subjects with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in [Table 13-4](#) below.

**Table 13-4 Criteria for notable vital sign abnormalities**

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

## **13.4 Electrocardiogram (ECG)**

The following quantitative variables will be summarized: ventricular rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc). Both Bazett (QTcB) and Fridericia (QTcF) corrections will be presented for QTc.

QTc will be summarized by computing the number and percentage of subjects (including 95% confidence intervals for pooled analyses, e.g. DMC or SCS) with:

- QTc > 500 msec
- QTc > 480 msec
- QTc > 450 msec
- QTc changes from baseline > 30 msec
- QTc changes from baseline > 60 msec
- PR > 250 msec

Summary statistics will be presented for ECG variables by visit and treatment group.

In addition, shift tables comparing baseline ECG interpretation (normal, abnormal, not available, total) with the worst on-study interpretation (normal, abnormal, not available, total) will be provided.

A listing of all newly occurring or worsening abnormalities will be provided, as well as a by-subject listing of all quantitative ECG parameters.

## **13.5 Immunogenicity**

A listing of immunogenicity (anti-AIN457 antibodies) will be provided.

## **13.6 Compound specific safety evaluation**

Safety topics of interest, such as risks defined in the Safety Profiling Plan, Risk Management Plan or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet that is stored in CREDI at the path Cabinets/CREDI Projects/A/AIN457A/Integrated Medical Safety.

The crude incidence and exposure-adjusted incidence rates for potential compound and class-related risks and routine risks will be summarized. In addition, listings will be provided presenting which subjects experienced which risk.

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

## **14 Sample size calculation**

The original power calculations used in the protocol have been updated to incorporate more recent published data in the PsA population. In addition, the statistical hierarchy (primary plus ranked secondary variables) was expanded to include more endpoints important in the treatment of psoriatic arthritis patients. No adjustment was made to the sample size as a result of the updated power calculations; the original sample size of N=200 per treatment regimen

was retained. The adjustments to the power calculations and the statistical hierarchy were done before the unblinding of the trial in order to prevent bias.

A 5% two-sided type I error rate will be used to control for type I error. Two secukinumab doses will be tested versus placebo with respect to the primary endpoint (ACR20 response at Week 24), thus the type-I-error will be split to 2.5% two-sided for each comparison. Sample sizes will be based on this type I error assumption.

A placebo response rate of about 25% after 24 weeks was reported for the TNF $\alpha$  inhibitor naïve population in the PSUMMIT I study ([McInnes et al 2013](#)), and 15% was reported for the TNF $\alpha$  inhibitor IR population in the PSUMMIT II study ([Ritchlin et al 2013](#)). Based on the weighted average, the overall placebo rate is expected to be 22%.

The response on secukinumab is expected to be 55% in the TNF $\alpha$  inhibitor naïve population and 35% in the TNF $\alpha$  inhibitor IR-population. Based on the weighted average, the overall rate on a dose of secukinumab is expected to be 49%.

For the primary endpoint, ACR20 in the overall population, 200 subjects per group would yield approximately 99% power to detect a treatment difference of 27% (Fisher's exact test, nQuery 7.0).

## **15 Power for analysis of secondary variables**

Power for secondary variables was calculated using a two-sided 2.5% type I error. With an assumed placebo rate of 7.6% and secukinumab 58.1%, the study is over 99% powered to detect a treatment difference of PASI75 in the full FAS population, assuming 135 subjects per treatment arm (Fisher's exact test, nQuery 7.0). Similarly, with an assumed placebo rate of 5% and secukinumab 44%, the study is over 99% powered to detect a treatment difference of PASI90 in the full FAS population, assuming 135 subjects per treatment arm. It is assumed that about 67.5% of enrolled patients have  $\geq 3\%$  skin involvement. Assumptions of PASI75 and PASI90 rates are based on PSUMMIT I and II studies (McInnes et al 2013 and Ritchlin et al 2013).

A difference of 1.31 and standard deviation of 1.34 has been observed for the change from baseline in DAS28-CRP in Golimumab (Kavanaugh et al 2009) for the TNF $\alpha$  inhibitor naïve population. Assuming the difference is half in the TNF $\alpha$  inhibitor IR population, the overall population has a difference of 1.12. With these assumptions, the study has approximately over 99% power to detect a difference between secukinumab and placebo (Two group t-test, nQuery Advisor 7.0), assuming 200 subjects per arm.

A standard deviation of approximately 10.1 and a treatment difference of 6.32 has been observed for the change from baseline at week 24 in SF36-PCS in Ustekinumab trial (McInnes et al 2013). Using those assumptions, the study has approximately 99% power to detect a difference between secukinumab and placebo (Two group t-test, NQuery Advisor 7.0), assuming 200 subjects per arm.

A standard deviation of approximately 0.5 and a treatment difference of 0.25 has been observed for the change from baseline at week 24 in HAQ-DI in Ustekinumab trial (McInnes et al 2013; Ritchlin et al 2012; Ritchlin et al 2013). Using those assumptions, the study has

approximately 99% power to detect a difference between secukinumab and placebo (Two group t-test, NQuery Advisor 7.0), assuming 200 subjects per arm.

With an assumed placebo rate of 7.4% (McInnes et al 2013 and Ritchlin et al 2013) and secukinumab 25.5%, the study is over 99% powered to detect a treatment difference of ACR50 in the full FAS population, assuming 200 subjects per treatment arm (Fisher's exact test, nQuery 7.0).

For structural endpoint, historical data (adalimumab) showed a standard deviation of 1.2 on active treatment and 2.4 on placebo at week 26, and a difference of 0.6 for the TNF $\alpha$  inhibitor naïve population. Assuming the difference is half in the TNF $\alpha$  inhibitor IR population, the overall population has a difference of 0.51. Using the above assumptions, there is 80% power to show statistically significant differences between secukinumab (pooled 400 subjects) and placebo (200 subjects). Individual comparisons between secukinumab and placebo would have 66% power (Satterthwaite t-test, nQuery 7.0).

For the presence of dactylitis at Week 24 in the subset of patients who have dactylitis at baseline, with an assumed placebo rate of 76% (McInnes et al 2013) and secukinumab 57%, there is about 89% power to show statistically significant difference between secukinumab (pooled 200 subjects) and placebo (100 subjects), assuming 50% patients have dactylitis at baseline (Fisher's exact test, nQuery 7.0).

For the presence of enthesitis at Week 24 in the subset of patients who have enthesitis at baseline, with an assumed placebo rate of 81% (McInnes et al 2013) and secukinumab 65%, there is about 87% power to show statistically significant difference between secukinumab (pooled 240 subjects) and placebo (120 subjects), assuming 60% patients have enthesitis at baseline (Fisher's exact test, nQuery 7.0).

## **16 Interim Analysis**

The Week 52 analysis will be performed after all subjects have completed the Week 52 visit. For this analysis, all subjects will have completed the assessments related to the primary and secondary objectives. Thus, no adjustment will be made to the type I error rate for this analysis and an interim clinical study report will be produced.

## **17 DMC**

A project-level DMC will monitor the trials' progress for unexpectedly large differences in toxicity between treatment groups on a regular basis or per the request of the DMC. Details regarding the reasons for the DMC and the grounds for stopping/continuing studies, as well as the DMC procedures are provided in the project-level DMC charter.

## **18 Appendix**

### **18.1 Visit Windows**

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

Of note, subjects are allowed to have gaps in visits. All data collected will be displayed in listings.





Week 84	589	576-603	562-617	562-617				562-617	562-617			
Week 88	617	604-631										
Week 92	645	632-659	618-687	618-687				618-687	618-687			
Week 96	673	660-687										
Week 100	701	688-715										
Week 104	729	716-743	688-743	688-743	450-743	548-743	548-743	688-743	688-743	548-743	632-743	548-743
<p>Group1: ACR components, Vital signs  Group2: Hematology, blood chemistry, urinalysis  Group3: MRI  Group4: X-Ray, WPAI-GH  Group5: PK  Group6: Presence of enthesitis, LEI, presence of dactylitis, LDI, dactylitis count  Group7: PASI, IGA, TLS, mNAPSI  Group8: SF-36, FACIT, PsAQoL, EQ-5D, DLQI  Group9: Lipids  Group10: ECG  * The first administration of randomized study treatment (first dose) is defined as 1.</p>												

The following rules are used to determine the window for an applicable visit post baseline: “Lower limit” = “upper limit of prior applicable visit” + 1. “Upper limit” = “target day of current visit” + integer part of (“target day of next applicable visit” – “target day of current visit”)/2. Lower limit of the first applicable visit is always Day 2.

The mapping described above applies to all visits (not just scheduled visits). Repeat and/or unscheduled visits (which will be numbered in the database according to new NCDS standards) will be mapped for analysis purposes in the same way as scheduled visits. This leaves the possibility, then, for multiple measurements within an analysis window. The following conventions will be used to determine the appropriate measurement to be summarized in the event of multiple measurements within a visit window.

**Table 18-2 Rules for flagging variables**

Timing of measurement	Type of data	Rule
Baseline	All data	The last measurement made prior to administration of the first dose of study treatment – note this may include measurements taken on the day of randomization (e.g. lab). If a patient did not receive any dose of study treatment then the randomization date will be used.
Post-baseline efficacy	All data	<ul style="list-style-type: none"> <li>• For visits without switch of treatment in the window, the measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g. 1 before target date and 1 after) the first one will be used.</li> <li>• For visits during which the patient switches from placebo to AIN the following will be done based on whether or not the patient met the rescue criteria: <ul style="list-style-type: none"> <li>○ If the analysis visit window is &lt;= week 16(for non-responders) or week 24 (for responders), then: <ul style="list-style-type: none"> <li>▪ If available, the closest measurement to the target date which is ON or BEFORE the switch date will be used (i.e. the closest measurement to target which is on placebo).</li> <li>▪ If there are no data on or before the switch then the closest measurement to the target date after the switch will be used.</li> </ul> </li> <li>○ If the analysis visit window is &gt; week 16(for non-responders) or week 24 (for responders), then <ul style="list-style-type: none"> <li>▪ If available, the closest measurement to the target date which is AFTER the switch date will be used (i.e. the closest measurement to target which is on AIN).</li> <li>▪ If there are no data AFTER the switch then the closest measurement to the target date before the switch will be used.</li> </ul> </li> </ul> </li> </ul>
Post-baseline safety	Summary visit information (e.g. lab, ECG, etc.)	<ul style="list-style-type: none"> <li>• For visits without switch of treatment in the window, the measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g. 1 before target date and 1 after) the first one will be used.</li> <li>• For visits during which the patient switches from placebo to AIN the following will be done based on whether or not the patient met the rescue criteria: <ul style="list-style-type: none"> <li>○ If the analysis visit window is &lt;= week 16(for non-responders) or week 24 (for responders), then: <ul style="list-style-type: none"> <li>▪ If available, the closest measurement to the target date which is ON or BEFORE the switch date will be used (i.e. the closest measurement to target which is on placebo).</li> <li>▪ If there are no data on or before the switch then the closest measurement to the target date after the switch will be used.</li> </ul> </li> </ul> </li> </ul>

Timing of measurement	Type of data	Rule
		<ul style="list-style-type: none"> <li>○ If the analysis visit window is &gt; week 16(for non-responders) or week 24 (for responders), then <ul style="list-style-type: none"> <li>▪ If available, the closest measurement to the target date which is AFTER the switch date will be used (i.e. the closest measurement to target which is on AIN).</li> <li>▪ If there are no data AFTER the switch then the closest measurement to the target date before the switch will be used.</li> </ul> </li> </ul>
Post-baseline safety	Notable abnormalities (e.g. lab)	The most extreme measurement in the window will be used. Note this means a patient can have a notably high and notably low measurement within a window.

## 18.2 Statistical methodology and assumptions

### 18.2.1 Analysis of continuous data

#### 18.2.1.1 Summary statistics for continuous data

Summary statistics (including N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum) will be provided for continuous data by visit and treatment group.

#### 18.2.1.2 Mixed-effects repeated measures model

Endpoints with continuous data type expected to be normally distributed (e.g. DAS28) will be analyzed using a mixed-effects repeated measures model (MMRM) with treatment regimen, randomization strata, and analysis visit as factors and weight and baseline as continuous covariates. Confidence intervals for the difference between each dose of secukinumba and placebo will be calculated.

SAS code for MMRM:

```
Proc mixed data= das28 covtest;
```

```
Class trt stratum;
```

```
Model response= trt weight stratum baseline/ s;
```

```
Repeated /type=un subject=patientid r;
```

```
Run;
```

#### 18.2.1.3 Non-parametric analysis of covariance

A non-parametric ANCOVA model (Koch 1998) will be used for the endpoints that are not normally distributed, e.g. X-ray, MRI, et. ctrl.

2-stage SAS code for non-parametric ANCOVA:

```
1) Proc glm data=xray;
```

```
by stratum;
```

```
Model response= weight baseline/ s;
```

```
Output out=results residual=resid;
```

```
Run;
```

```
2) proc freq data=tmp; *tmp is the data "results" combined with strata and trt information;
Tables strata*trt*resid/cmh;
Run;
```

## 18.2.2 Analysis of binary (and categorical) data

### 18.2.2.1 Summary statistics for binary and categorical data

Summary statistics for discrete variables will be presented in contingency tables and will include count and frequency in each category. If applicable, confidence intervals will be derived as well based on the score method including continuity correction [Newcombe (1998)]:

With  $z$  as  $(1-\alpha/2)$ -quantile of the standard normal distribution (SAS:  $z=\text{PROBIT}(1-\alpha/2)$ ),  $n$  as total number of subjects (i.e. number of subjects in the denominator), and  $p$  as estimated crude incidence (number of subjects with event /  $n$ ) it is  $q = 1 - p$

Then the lower limit is

$$L = 100 \times \max \left( 0, \frac{2np + z^2 - 1 - z \sqrt{z^2 - 2 - \frac{1}{n} + 4p(nq + 1)}}{2(n + z^2)} \right)$$

and the upper limit is

$$U = 100 \times \min \left( 1, \frac{2np + z^2 + 1 + z \sqrt{z^2 + 2 - \frac{1}{n} + 4p(nq - 1)}}{2(n + z^2)} \right).$$

For binary response variables (e.g. for ACR20/50/70, HAQ-DI responder, PASI 75, IGA response) the placebo-adjusted response rates including 95% confidence interval will be derived.

SAS code for risk difference:

```
Proc freq data=acr order=formatted;
Tables response*trt/ riskdiff;
Run;
```

(Note the response value should be sorted with '1' ahead of '0'.)

Fisher's exact test will be applied to rare events (e.g., MCR), pairwise treatment group comparisons to placebo or active controls.

SAS code for Fisher's exact test:

```
Proc freq data=mcr order=formmatted;
Tables response*trt/Fisher;
Run;
```

Figures will be provided for primary and secondary variables, with means and 95% confidence intervals displayed across time for all the treatment groups.

### **18.2.2.2 Logistic regression**

Certain binary outcome variables, e.g. response outcomes, will be evaluated using a logistic regression model with treatment regimen, weight, stratum if applicable. Odds ratios will be computed for comparisons of AIN457 regimens versus control(s) utilizing the logistic regression model fitted.

SAS code for logistic regression:

```
Proc logistic data=acr descending;
```

```
Class trt stratum;
```

```
Model response=trt weight stratum;
```

```
Run;
```

To assess potential region effect for the primary variables or key secondary variables, a logistic regression model will be fitted with treatment, region, weight, stratum if applicable, treatment-by-region interaction as explanatory variables. If  $p < 0.100$  for the treatment-by-region interaction, then, further exploratory analysis will be done (tabular and/or graphical methods) to look for a possible explanation of the differences observed across regions.

### **18.2.3 Multiple Imputation**

A multiple imputation will be performed based on MAR by treatment group for baseline weight, baseline and post-baseline of each parameter for visits up to the primary time point (Week 24) using Markov Chain Monte Carlo (MCMC) method with EM algorithm.

Impute the missing values 100 times (NIMPUTE) with a seed=457<studycode> as shown below:

```
proc mi data=min max=out=imp minmaxiter=1000000 nimpute=100 seed=4572306;
```

```
by trt;
```

```
var weight_base var1_base var1_week1-var1_week24;
```

```
mcmc chain=multiple initial=em;
```

```
run;
```

If needed repeat for each component necessary to calculate the final score, e.g. as follows:

```
proc mi data=imp min=<min of scale> max=<max of scale> out=imp2 minmaxiter=100000  
nimpute=1 seed=4572306;
```

```
by trt _imputation_;
```

```
var weight_base var2_base var2_week1-var2_week24;
```

```
mcmc chain=multiple initial=em;
```

```
run;
```

The score can now be calculated based on the complete data. MIANALYZE will then be performed with the contrast estimate and the corresponding standard error. These are derived using GENMOD as shown below:

```
proc genmod data = imp2;
  by _imputation_;
  class trt strata;
  model var = trt base_wgt strata / link=logit dist=bin;
  lsmeans trt / diff;
  estimate 'AIN457 75mg mg vs Placebo' trt 1 -1 0;
  estimate 'AIN457 150mg mg vs Placebo' trt 1 0 -1;
  ods output Estimates=imp_est lsmeans=imp_lsm diffs=imp_lsm_diff;
run;
```

The estimates and the standard errors of imputed parameter will then be combined by applying Rubin's rules for multiple imputed data sets.

```
proc mianalyze data=imp_est;
  by label;
  modeleffects LBetaEstimate;
  stderr StdErr;
  ods output ParameterEstimates=mi_res;
run;
```

## 18.2.4 Crude incidence and related risk estimates

### 18.2.4.1 Crude incidence and 100\*(1- $\alpha$ )% confidence interval

For  $n$  subjects, each at risk to experience a certain event with probability  $\pi$ , the crude incidence is estimated as  $p=x/n$ , where  $x$  is the number of subjects with the event.

Absolute and relative frequencies will be displayed as well as 95% confidence interval for the relative frequency based on the score method including continuity correction (Newcombe 1998).

With  $z$  as  $(1-\alpha/2)$ -quantile of the standard normal distribution (SAS:  $z=\text{PROBIT}(1-\alpha/2)$ ),  $n$  as total number of subjects (i.e. number of subjects in the denominator), and  $p$  as estimated crude incidence (number of subjects with event /  $n$ ) it is  $q = 1 - p$ .

Then the lower limit is

$$L = \max \left( 0, \frac{2np + z^2 - 1 - z \sqrt{z^2 - 2 - \frac{1}{n} + 4p(nq + 1)}}{2(n + z^2)} \right)$$

and the upper limit is

$$U = \min \left( 1, \frac{2np + z^2 + 1 + z \sqrt{z^2 + 2 - \frac{1}{n} + 4p(nq - 1)}}{2(n + z^2)} \right)$$

Note: if  $p = 0$  then  $L = 0$  and if  $p = 1$  then  $U = 1$ .

If appropriate, an exact  $100*(1-\alpha)\%$  confidence interval (Clopper-Pearson 1934) will be obtained by using the SAS procedure PROC FREQ with the EXACT BINOMIAL statement. However, the confidence interval derived via the score method including continuity correction will be the default in safety analyses.

#### **18.2.4.2 Odds ratio and $100*(1-\alpha)\%$ confidence interval**

For an investigational drug group with  $n_1$  subjects at risk, independent from the control group (e.g. placebo or comparator) with  $n_0$  subjects at risk, of whom  $x_1$  and  $x_0$  experience a certain event with probability  $\pi_1$  and  $\pi_0$  respectively, the odds ratio is estimated as

$$\frac{p_1/(1-p_1)}{p_0/(1-p_0)} \quad \text{with } p_1 = x_1/n_1 \text{ and } p_0 = x_0/n_0.$$

A conditional exact  $100*(1-\alpha)\%$  confidence interval will be obtained by using the SAS procedure PROC FREQ with statement EXACT OR.

#### **18.2.4.3 Risk difference and $100*(1-\alpha)\%$ confidence interval**

For an investigational drug group with  $n_1$  subjects at risk, independent from the control group (e.g. placebo or comparator) with  $n_0$  subjects at risk, of whom  $x_1$  and  $x_0$  experience a certain event, the risk difference is estimated as  $p_1 - p_0$  with  $p_1 = x_1/n_1$  and  $p_0 = x_0/n_0$ .

Exact unconditional confidence limits for the risk difference will be obtained with SAS procedure PROC FREQ and option RISKDIFF in the TABLES statement, specifying the RISKDIFF option also in the EXACT statement.

### **18.2.5 Exposure adjusted incidence rate and related risk estimates**

#### **18.2.5.1 Exposure adjusted incidence rate and $100*(1-\alpha)\%$ confidence interval**

It will be assumed that for each of  $n$  subjects in a clinical trial the time  $t_j$  ( $j=1, \dots, n$ ) to the first occurrence of a certain event is observed, or if the event was not experienced, the (censored) time to the end of the observation period. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity  $\theta$ . The rate

parameter  $\theta$  will be estimated as  $\lambda = D/T$ , where  $T = \sum_{j=1}^n t_j$  and  $D$  is the number of subjects

with at least one event. Conditionally on  $T$ , an exact  $100*(1-\alpha)\%$  confidence interval for a Poisson variable with parameter  $\theta T$  and observed value  $D$  can be obtained based on (Garwood, 1936), from which an exact  $100*(1-\alpha)\%$  confidence interval for  $D/T$  will be derived as follows (Sahai, 1993; Ulm, 1990):

Lower confidence limit  $L = \frac{0.5c_{\alpha/2, 2D}}{T}$  for  $D > 0$ , 0 otherwise,

Upper confidence limit  $U = \frac{0.5c_{1-\alpha/2, 2D+2}}{T}$

where  $c_{\alpha, k}$  is the  $\alpha$ th quantile of the Chi-square distribution with  $k$  degrees of freedom.

The example below shows how this should be handled for cases where subjects switch treatment. In particular for summarizing ‘Any AIN’ as a group, one should take into consideration the sequence of treatments while calculating exposure time for subjects.

**Table 18-3 Examples for calculating exposure time for incidence rates (IR)**

1st treatment	1st exposure	2nd treatment	2nd exposure	Event days (in terms of study day)	Exposure for IR
Placebo	100 days	150 mg	200 days	50 (1st trt) 110 (10 days into 2nd trt)	Placebo: 50 days (event) 150 mg: 10 days (event) Any AIN: 10 days (event)



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Clinical Development

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457F2306

**A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active psoriatic arthritis**

### **RAP Module 3 – Detailed Statistical Methodology**

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## List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALT/GPT	Alanine aminotransferase/glutamic pyruvic transaminase
ANA	Anti-nuclear antibodies
Anti-CCP	Anti-cyclic citrullinated peptide
AS	Ankylosing Spondylitis
AST/GOT	Aspartate aminotransferase/glutamic oxaloacetic transaminase
BME	Bone Marrow Edema
BMI	Body Mass Index
BSL	Baseline
CASPAR	CIASSification criteria for Psoriatic ARthritis
CFR	Code of Federal Regulations (US)
CRF	Case Report/Record Form
CRD	Clinical Research and Development
CPO	Country Pharma Organization
CRO	Contract Research Organization
CRP/hsCRP	C-reactive protein / high sensitivity C-reactive protein
CSR	Clinical Study Report
CTEP	Cancer Therapy Evaluation Program
DAS	Disease Activity Score
DMARD	Disease Modifying Antirheumatic Drug
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic acid
DS&E	Drug Safety and Epidemiology
dsDNA	Anti-double stranded DNA antibodies
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EMA/EMEA	European Medicines (Evaluation) Agency

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EULAR	European League Against Rheumatism
ESR	Erythrocyte Sedimentation Rate
FACIT-Fatigue <sup>®</sup>	Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GEE	Generalized estimating equation
HAQ-DI <sup>®</sup>	Health Assessment Questionnaire – Disability Index
HIV	Human Immunodeficiency Virus
HRQoL	Health-related Quality of Life
hsCRP	High sensitivity C-Reactive Protein
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGA mod 2011	Novartis Investigator’s Global Assessment modified 2011
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	IntraUterine Device
IUS	IntraUterine System
i.v.	intravenous(ly)
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDI	Leeds Dactylitis Index
LDL	Low Density Lipoprotein
LEI	Leeds Enthesitis Index
LLN	Lower limit of normal
LOCF	Last observation carried forward
LLOQ	Lower Limit of quantification
MCR	Major Clinical Response
MCS	Mental Component Summary

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MedDRA	Medical Dictionary for Regulatory Activities
MRD	Mean relative difference
mmHg	Millimeter mercury
MMP	Matrix Metalloprotease
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PG	Pharmacogenetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PoC	Proof of Concept
PPD	Purified protein derivative
PRN	As required
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
PsAMRIS	Psoriatic Arthritis Magnetic Resonance Imaging Scoring System
PsAQoL	Psoriatic Arthritis Quality of Life questionnaire
QoL	Quality of Life
RA	Rheumatoid Arthritis
RBC	Red Blood Cells
RF	Rheumatoid Factor
SAE	Serious adverse event
s.c.	subcutaneous(ly)
SCR	Screening
SF-36	Medical Outcome Short Form (36) Health Survey
SJC	Swollen Joint Count
SNP	Single Nucleotide Polymorphism
SpA	Spondyloarthritides
SWFI	Sterile water for injection
t.i.d.	ter in die, three times daily
TJC	Tender Joint Count

TNF	Tumor necrosis factor
TNF-IR	TNF $\alpha$ Inhibitor Incomplete Responders
ULN	Upper limit of normal
US	Unites States of America
VAS	Visual Analog Scale
WBC	White Blood Cells
WHO	World Health Organization
WPAI-GH	Work Productivity and Activity Impairment–General Health questionnaire

## 1 Introduction

Data will be analyzed by Novartis according to the data analysis section 9 of the clinical study protocol. That statistical methodology is described below and any deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section.

## 2 Study Objectives

The primary objective is to demonstrate the efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo in patients with active PsA based on the proportion of patients achieving an ACR20 response in the entire study population.

The secondary objectives of the study are to demonstrate:

- The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving a PASI75 response in the subgroup of subjects who have  $\geq 3\%$  skin involvement.
- The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving a PASI90 response in the subgroup of subjects who have  $\geq 3\%$  skin involvement.
- The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the DAS28-CRP at Week 24 in the entire study population.
- The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the SF36-PCS at Week 24 in the entire study population.
- The improvement (change) from baseline on secukinumab 75 or 150 mg is superior to placebo for the HAQ-DI at Week 24 in the entire study population.
- The efficacy of secukinumab 75 or 150 mg at Week 24 is superior to placebo based on the proportion of subjects achieving an ACR50 response in the entire study population.
- The improvement (change) from baseline to Week 24 on secukinumab pooled regimen (75 mg and 150 mg s.c.) is superior to placebo for joint/bone structural damage (van der Heijde modified total Sharp score) in the entire study population.
- The efficacy of secukinumab pooled regimen (75 mg and 150 mg s.c.) at Week 24 is superior to placebo based on the proportion of subjects with dactylitis in the subset of subjects who have dactylitis at baseline.
- The efficacy of secukinumab pooled regimen (75 mg and 150 mg s.c.) at Week 24 is superior to placebo based on the proportion of subjects with enthesitis in the subset of subjects who have enthesitis at baseline.
- The improvement (change) from baseline to Week 24 on secukinumab 75 or 150 mg is superior to placebo for joint/bone structural damage (van der Heijde modified total Sharp score) in the entire study population.

Furthermore, additional aspects of efficacy, safety and tolerability of secukinumab will be investigated.

### **3 Data presentation**

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

If not otherwise specified, p-values and confidence intervals will be two-sided.

Unless otherwise stated, the level of significance will be set to 5% (two-sided, family-wise type-I-error).

Data analyses will be presented by treatment regimen. Efficacy and safety data for the placebo-controlled period will be presented by the following 3 treatment groups. Subjects may be included in more than one treatment group for some analyses (e.g. exposure-adjusted adverse events over the entire treatment period). These treatment groups represent the regimens subjects will be eligible to be randomized to for the first 24 weeks of the study.

- Secukinumab regimen 1: secukinumab i.v. (10mg/kg) at BSL, Week 2 and Week 4 then secukinumab 75 mg s.c. starting at Week 8 and injected every 4 weeks
- Secukinumab regimen 2: secukinumab i.v. (10mg/kg) at BSL, Week 2 and Week 4 then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks
- Placebo regimen: Placebo i.v. at BSL, Week 2 and Week 4 then placebo s.c. starting at Week 8 and injected every 4 weeks

Note that the treatment groups above 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 4.2](#) for details).

#### **Comparative efficacy data**

Comparative efficacy analyses (i.e. inferential efficacy comparisons with placebo or active comparator) will focus on the time period when both active drug and the placebo are given in a manner suitable for making comparisons (e.g. double-blind). For AIN457F2306 this is the first 24-weeks of treatment. Comparative efficacy will be performed based on the FAS population using the randomized treatment. After week 24, the active secukinumab regimens will be compared using confidence intervals on the FAS population using treatment sequence.

#### **Efficacy data following rescue/re-randomization**

Data will also be presented after Week 24, by a combination of the ‘original’ and ‘switch’ treatment groups and will be referred to as treatment sequence. These treatment sequences represent the treatment combinations the subjects experience over the course of the entire trial in case of rescue or re-randomization.

All listings will be presented by treatment sequence.

## **4 Subjects and treatments**

### **4.1 Analysis Sets**

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

**Randomized set:** The randomized set will be defined as all subjects who were randomized. Unless otherwise specified, mis-randomized subjects (mis-randomized in IWRS/IVRS/IXRS) 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 patients 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 actual stratum, if stratified randomization is used.

**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.

### **4.2 Treatment groups**

The summaries by treatment will be performed by the randomized treatment or treatment sequence. For some safety summaries (e.g. exposure-adjusted) the 'switch' treatment may be summarized separately

- Randomized treatment:
  - AIN457 10 mg/kg - 75 mg
  - AIN457 10 mg/kg - 150 mg
  - Placebo
- Treatment sequence:
  - AIN457 10 mg/kg - 75 mg
  - AIN457 10 mg/kg - 150 mg
  - Placebo (non-responder) - AIN457 75 mg
  - Placebo (non-responder) - AIN457 150 mg
  - Placebo (responder) - AIN457 75 mg
  - Placebo (responder) - AIN457 150 mg
- Switch treatments (for placebo patients who cross-over):
  - AIN457 75 mg no load
  - AIN457 150 mg no load



## **5 Subgroup definitions**

The primary endpoint(s) and secondary endpoints will be evaluated for TNF-alpha inhibitor status.

## **6 Assessment windows, baseline and post baseline definitions, missing data handling**

### **Baseline and post-baseline definitions**

In general (except for X-ray and MRI structure data), a *baseline* value refers to the last measurement made prior to administration of the first dose of study treatment. A post-baseline value refers to a measurement taken after the first dose of study treatment. For X-ray, a baseline value is the last measurement prior to dosing if available, or the first value within 30 days post dosing if no value available prior to dosing. For MRI, a baseline value is the last measurement prior to dosing if available, or a value within 7 days post dosing if no value available prior to dosing.

### **Analysis visit windows**

*Analysis visit windows* will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are protocol defined scheduled visits around which analysis visit windows were created to cover the complete range of days within the study. The analysis visit windows and rules for dealing with multiple measurements within the windows are described in the [Appendix](#).

## **7 Subject disposition, background and demographic characteristics**

### **7.1 Subject disposition**

The number of subjects screened will be presented. In addition, the reasons for screen failures will be provided. The number and percentage of subjects in the randomized set who completed the study periods and who discontinued the study prematurely (including the reason for discontinuation) will be presented at the end of each treatment period (Week 52 and Week 104), if appropriate, for each treatment group and all subjects.

The number and percentage of patients who meet the rescue criteria at week 16 will be presented.

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

## **7.2 Background and demographic characteristics**

The following common background and demographic variables, if collected, will be analyzed in all studies:

### **Continuous variables:**

- Age (which is derived from date of birth and the screening assessment date)
- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)<sup>2</sup>

### **Categorical variables:**

- Age categories (<65 years, 65 years and older, 75 years and older)
- Gender
- Race
- Ethnicity

The following disease specific baseline characteristics and history of disease will be summarized as well:

- CASPAR, TNF $\alpha$  history (naive or inadequate responder), ACR components, number of prior biologic PsA therapies, MTX use (yes or no) and dose at baseline, time since first diagnosis of PsA, and psoriasis involvement (proportion of patients with psoriasis of hands and feet, psoriasis of the nail, and target lesion diameter).

Unless otherwise specified, summary statistics will be presented for continuous variables for each treatment group and for all subjects (total) 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 (total) in the randomized set.

## **8 Medical history**

Any condition entered on the *Relevant medical history / current medical conditions* CRF will be coded using the MedDRA dictionary. They will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. Summaries for cardiovascular medical history and psoriasis history will be provided as well.

Smoking history will be summarized by treatment group.

Chest x-ray (screening) results will be listed.

Unless otherwise specified, analyses will be based on the randomized set.

## **9 Study medication**

The analysis of study treatment data will be based on the safety set. The number of active and placebo infusions and injections will be summarized 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,  $\geq 1$  week,  $\geq 2$  weeks,  $\geq 3$  weeks,  $\geq 4$  weeks,  $\geq 8$  weeks, etc.) will be presented.

Duration of exposure will be defined as the time from first dose of study treatment to the time of treatment switch (for subjects who switch treatment) or end of treatment period (whichever is first). For subjects who discontinue, this will be the subject's last visit in the corresponding treatment period.

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

Duration of exposure (100 subject years) = duration of exposure (years) / 100

The analyses of duration of exposure described above will be done for the entire study treatment period.

## **10 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-baseline 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 surgeries and procedures will be summarized by primary system organ class and MedDRA preferred term.

The number and percentage of subjects receiving prior and concomitant psoriatic arthritis 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) and the total duration of exposure to psoriatic arthritis therapies previously.

Prior or concomitant medication will be identified by comparing recorded or imputed start and end dates of medication taken to the reference start date. Further rules will be given in RAP Module 8.

## 11 Efficacy evaluation

### 11.1 Description of efficacy variables

#### ACR 20/50/70

ACR20 is a binary response variable defined for each subject. A subject will be considered a responder according to ACR20 criteria if he/she has at least (i.e.,  $\geq$ ):

- 20% improvement from baseline in tender 78-joint count
- 20% improvement from baseline in swollen 76-joint count
- 20% improvement from baseline in at least 3 of the following 5 measures:
  - Patient's assessment of PsA pain (VAS 100 mm)
  - Patient's global assessment of PsA disease activity (VAS 100 mm)
  - Physician's global assessment of PsA disease activity (VAS 100 mm)
  - Patient self-assessed disability (Health Assessment Questionnaire [HAQ©] score)
  - Acute phase reactant (C-reactive protein [hsCRP]) **or** Erythrocyte sedimentation rate (ESR).

In the definition above, the *baseline* value refers to the last measurement made prior to administration of the first dose of study treatment.

The primary endpoint is the proportion of subjects achieving ACR20 at Week 24. Primarily, CRP will be used to calculate ACR response: ESR will only be used in the event CRP is missing.

ACR50 and ACR70 are defined in the same way as ACR20 by replacing the 20% with 50% and 70% improvement from baseline, respectively.

ACR<sub>n</sub> represents the percent improvement on the continuous scale and from ACR<sub>n</sub> one can directly calculate ACR20, ACR50, and ACR70 using the appropriate cutoffs. This variable is defined as:

$ACR_n = \min(x_1, x_2, x_3)$ , where

$x_1$  = % improvement from baseline in tender 68-joint count

$x_2$  = % improvement from baseline in swollen 66-joint count

and  $x_3$  = 3<sup>rd</sup> largest value of  $x_4, x_5, x_6, x_7, x_8$  where,

$x_4$  = % improvement from baseline in Patient's assessment of PsA pain (VAS 100 mm)

$x_5$  = % improvement from baseline in Patient's global assessment of PsA disease activity (VAS 100 mm)

$x_6$  = % improvement from baseline in Physician's global assessment of PsA disease activity (VAS 100 mm)

$x_7$  = % improvement from baseline in Patient self-assessed disability (Health Assessment Questionnaire [HAQ©] score)

$x_8$  = % improvement from baseline in Acute phase reactant (C-reactive protein [hsCRP]) or Erythrocyte sedimentation rate (ESR)

ACRn can be computed even if up to two values of  $x_4$ ,  $x_5$ ,  $x_6$ ,  $x_7$ ,  $x_8$  are missing. ACRn, theoretically, can not be computed, if one or both of  $x_1$ ,  $x_2$  is/are missing OR more than three values of  $x_4$ ,  $x_5$ ,  $x_6$ ,  $x_7$ ,  $x_8$  are missing.

### **Health Assessment Questionnaire - Disability Index (HAQ-DI)**

The Health Assessment Questionnaire (HAQ©) 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 (Health Assessment Questionnaire – Disability Index), 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].

Scoring for the eight functional categories and overall disability index scoring will be performed as follows:

There are eight categories; first score within each category:

- Dressing and Grooming, includes items 1 and 2
- Arising, includes items 3 and 4
- Eating, includes items 5, 6 and 7
- Walking, includes items 8 and 9
- Hygiene, includes items 10, 11, and 12
- Reach, includes items 13 and 14
- Grip, includes items 15, 16 and 17
- Activities, includes items 18, 19, and 20

The score for each category will be the single response within the category with the highest score (greatest difficulty). For example, in the "Eating" category, there are two answers (one for each item). If "Cut your food with a knife or fork" is marked as "3" and "Lift a full cup or glass to your mouth" is marked as "0", then the score for the "Eating" category would be "3" (the response indicating the greatest difficulty within the category). If a component question is left blank or the response is too ambiguous to assign a score, then the score that that category will be determined by the remaining completed question(s). However, if **any** "aids or devices" and/or "help from another person" items at the bottom of each page are checked, the category to which they apply will be adjusted upward to "2". If the basic score is **already** "2" or "3", the score remains unchanged. "Aids or devices" and "help from another person" can **only** change a category's score to "2"; they do **not** change the score to a "1" or a "3".

The score for the disability index will be the mean of the eight category scores. If more than two of the categories, or 25%, are missing, scale will not be scored. Otherwise, divide the sum of the categories by the number of answered categories. The higher score indicates greater disability.

**HAQ-DI response** is defined by an improvement of at least 0.3 score points compared to baseline.

### **Joint/bone structural damage**

The primary score for analyses will be total van der Heijde modified Sharpe (vdH-S) score (van der Heijde 1999), but the erosion score and joint space narrowing score will be analyzed in similar fashion.

Erosions will be assessed each hand (20 locations per hand) and each foot (6 locations per foot). The maximum erosion score is 200 for all 40 hand locations, and 120 for all 12 feet locations. Thus, the total possible erosion score is 320.

Joint space narrowing (JSN) will be assessed in each hand (20 locations per hand) and foot (6 locations per foot). The maximum score is 160 for all 40 hand joints, and 48 for all 12 feet joints. Thus, the total possible JSN score is 208.

**Pencil-in-cup:** Osteolysis of the proximal phalanx and the base of the distal phalanx resulting in a pencil like proximal phalanx covered by cup like base of the distal phalanx. Pencil-in-cup will be scored as “P” where applicable.

**Gross Osteolysis:** Osteolysis of the phalanx resulting in a loss of the normal joint structure, usually accompanied by shortening of the length of the phalanx. Gross osteolysis will be scored as “G” where applicable.

If a joint or bone is not visible (e.g. poor film quality, missing imaging, severe misalignment, flexion deformity, dislocation) at the timepoint, the individual joint or bone will be coded as Not Visible (N).

If radiographs at the timepoint show a joint or bone with surgical fusion, replacement (prosthesis), or amputation, then the joint or bone will be scored Surgically Modified (S).

To obtain the total vdH-S score, scores for erosions and JSN in both the hands and feet will be added together. Any “P” or “G” will be considered the maximal score for the feature (erosions and JSN) per location in the calculation of the total vdH-S score. Any “N” or “S” will be considered null in the calculation of the total vdH-S score. The range of scores is 0 ~ 528.

The joints are divided into 10 segments according to Table 11-1. In each segment an adequacy threshold is defined. For each segment, when the change from baseline values are available for at least the threshold number of joints, the change from baseline will be calculated for the segment, with missing joints imputed by the within-segment mean change over individual joints. Otherwise (i.e. if less than threshold number of joints have available change from baseline values), the segment change from baseline will be missing. When  $\geq 5$  segments have evaluable change from baseline values, the overall change from baseline value will be calculated, with missing segments imputed by the mean change over segments. Otherwise (i.e. if  $\leq 4$  segments have evaluable change from baseline values), the overall change from baseline value will be missing.

**Table 11-1 Segmental distribution**

Segment	Total number of joints	Adequacy threshold	Joints at one side
PIP erosions	8	5	PIP2, PIP3, PIP4, PIP5
DIP erosions	8	5	DIP2, DIP3, DIP4, DIP5
MCP + thumb erosions	12	7	MCP1, MCP2, MCP3, MCP4, MCP5, INTERPHALANGEAL JOINT OF THE HAND
Wrist erosions	12	7	FIRST METACARPAL BONE, DISTAL RADIUS, DISTAL ULNA, TRAPEZOID-TRAPEZIUM, NAVICULAR BONE, LUNATE BONE
Foot erosions	12	7	MTP1, MTP2, MTP3, MTP4, MTP5, INTERPHALANGEAL JOINT 1
PIP JSN	8	5	PIP2, PIP3, PIP4, PIP5
DIP JSN	8	5	DIP2, DIP3, DIP4, DIP5
MCP + thumb JSN	12	7	MCP1, MCP2, MCP3, MCP4, MCP5, INTERPHALANGEAL JOINT OF THE HAND
Wrist JSN	12	7	CMC3, CMC4, CMC5, RADIOCARPAL, SCAPHOID-TRAPEZIUM, CAPITATE-NAVICULAR-LUNATE
Foot JSN	12	7	MTP1, MTP2, MTP3, MTP4, MTP5, INTERPHALANGEAL JOINT 1

The readings of the x-rays and the scoring will be performed centrally. Two central independent radiograph readers, both blinded to treatment arm and radiograph sequence, will analyze the digitized images. In the case that adjudication is needed, a third consensus read will be performed. The statistical analysis will use the adjudicated score, if available, or the average score from the two readers otherwise.

### Major clinical response

Major clinical response is defined as continuous six-months of ACR70 response for a subject.

### DAS28, low disease activity and remission

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

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

The following 28 joints will be assessed for tenderness and swelling: metacarpophalangeal IV(10), thumb interphalangeal (2), hand proximal interphalangeal II-V (8), wrist (2), elbow(2), shoulders (2), and knees (2).

The following formulas can be used to calculate the DAS28 with CRP (mg/L) or ESR (mm/hour).

$$\text{DAS28-CRP} = 0.56 \cdot \sqrt{\text{TJC28}} + 0.28 \cdot \sqrt{\text{SJC28}} + 0.36 \cdot \ln(\text{CRP}+1) + 0.014 \cdot \text{PGA} + 0.96$$

$$\text{DAS28-ESR} = 0.56 \cdot \sqrt{\text{tender28}} + 0.28 \cdot \sqrt{\text{swollen28}} + 0.70 \cdot \ln(\text{ESR}) + 0.014 \cdot \text{PGA}$$

*TJC28: 28 Tender joint count; SJC28: 28 Swollen joint count; CRP: C-reactive protein; PGA: Patient Global Assessment*

If any component measurement is missing, DAS28 will be missing.

DAS28-CRP will be primary for analysis; DAS-ESR will be secondary.

DAS28-CRP (or ESR) remission is defined as a DAS28-CRP (or ESR) index score less than 2.6. Low disease activity is defined as DAS28-CRP (or ESR) index less than or equal to 3.2.

### **EULAR response**

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

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

**Table 11-2 EULAR response criteria**

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

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

### **Minimal disease activity**

A subject will be considered a responder of minimal disease activity (MDA, see [Coates 2010](#)) if he/she achieves at least 5 of the following 7 items:

- ≤ 1 tender joint count



- $\leq 1$  swollen joint count
- PASI  $\leq 1$  or IGA  $\leq 1$
- patient pain VAS  $\leq 15$
- patient global VAS  $\leq 20$
- HAQ-DI  $\leq 0.5$
- tender enthesal points  $\leq 1$

## **ACR Components**

### ***Tender 78 joint count and swollen 76 joint count***

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

If the number of joints for which data were available (e.g., T) is less than 78/76 for the tender/swollen joint assessment, the number of tender/swollen joints (e.g., t) will be scaled up proportionately (i.e.,  $78*t/T$  or  $76*t/T$  for tender or swollen joint count).

### ***Patient's assessment of PsA Pain***

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*".

### ***Patient's global assessment of PsA 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*".

### ***Physician's global assessment of PsA 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 patient.

### ***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.

### ***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.

### **Magnetic Resonance Imaging**

Magnetic Resonance Imaging (MRI) will be performed in a subgroup of subjects with at least one swollen wrist at baseline at selected sites. The independent reviewers shall perform MRI assessments according to the modified PsAMRIS scoring method (Ostergaard, Mikkelsen et al 2009). Assessments will be performed on the hand with the more swollen wrist determined at baseline by the investigator. If both wrists are equally affected, the dominant hand/wrist will be chosen. The MRIs will be scored for the following assessments:

- Synovitis
- Tenosynovitis
- Periarticular inflammation
- Bone edema/osteitis
- Bone erosion
- Bone proliferation
- Joint space narrowing

Synovitis is defined as an area in the synovial compartment that shows greater than normal postgadolinium enhancement of a thickness greater than the estimated width of the normal synovium. A total of 17 locations in the hand and wrist will be evaluated for synovitis. Synovitis will be assessed on a scale of 0-3 for each location. The maximum possible score for synovitis is 51.

Tenosynovitis is defined as an area with signal characteristics that show greater than normal water content or greater than normal post-gadolinium enhancement adjacent to a tendon, in an area with tendon sheath. A total of 14 hand locations and 10 wrist regions will be evaluated for tenosynovitis. Synovitis will be assessed on a scale of 0-3 for each location. The maximum possible score for tenosynovitis in the hand and wrist is 72.

Periarticular inflammation is defined as an area with signal characteristics that show greater than normal water content or greater than normal post-gadolinium enhancement at extraarticular sites including the periosteum and the entheses (not including tendon sheaths as this is defined as tenosynovitis). A total of 28 locations in the hand will be evaluated for periarticular inflammation. Periarticular inflammation will be assessed on a scale of 0-2 for each location. The maximum possible score for periarticular inflammation in the hand is 56.

MRI edema/osteitis is defined as a lesion, that may occur alone or surrounding an erosion or other bone abnormalities, within the trabecular bone, often with ill-defined margins and signal characteristics consistent with increased water. A total of 43 locations will be evaluated for bone edema/osteitis. Bone edema/osteitis is scored on a scale of 0-3 based on the proportion of estimated originally noneroded bone involved. The maximum possible score for bone edema/osteitis is 129.

MRI bone erosion is defined as a sharply marginated bone lesion, with correct juxta-articular localization and typical signal characteristics, with a cortical break seen in at least one plane. A total of 43 locations will be evaluated for bone erosions. Each bone is scored on a scale of 0-10. The maximum possible score for bone erosions is 430.

Bone proliferation is defined as an abnormal bone formation in the periarticular region such as at the entheses and across the joint. A total of 14 joints will be evaluated for bone proliferation. Bone proliferation will be assessed on a scale of 0-2 for each location. The maximum possible score for Bone proliferation is 28.

Joint space narrowing (JSN) is defined as the reduction in joint space. JSN is scored on a scale of 0-4 based on the amount of narrowing present in a given joint. The maximum possible score for JSN in all 29 hand joints is 116.

If a joint or bone is not visible (e.g. poor image quality, missing imaging, severe misalignment, flexion deformity, dislocation, ankylosis of >50% of articular surface [for erosion score only]) at the timepoint, the individual joint or bone will be coded as Not Visible (N). If MRIs at the timepoint show a joint or bone with surgical fusion, replacement (prosthesis), or amputation, then the joint or bone will be scored Surgically Modified (S). To obtain the total score per feature, any "N" or "S" will be considered null in the calculation.

The score per feature will be calculated as the sum of scores from all available locations per feature.

### **PsARC response**

A subject is defined as a PsARC responder if, and only if, they have an improvement in two of the following four factors (with at least one factor being a joint count) and no worsening in the remaining factors

- Patient global assessment (0-100 mm VAS scale, improvement defined as decrease of at least 20 mm)
- Physician global assessment (0-100 mm VAS scale, improvement defined as decrease of at least 20 mm)
- Tender 78-joint count (improvement defined as decrease of at least 30%)
- Swollen 76-joint count (improvement defined as decrease of at least 30%)

PsARC response won't be calculated if any of the four components are missing.

### **Leeds Enthesitis Index (LEI)**

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. Tenderness on examination is recorded as either present (1) or absent (0) for each of the 6 sites, for an overall score range of 0–6. Higher count represents greater enthesitis burden.

In this study, the lateral condyle femur L + R data were collected instead of required medial condyle femur L + R. Therefore, a 4-site LEI (LEI-4) will be calculated with the four correct sites: lateral epicondyle humerus L + R, proximal achilles L + R. If measures are missing for any of these four sites, the LEI-4 won't be calculated.

### **Presence of enthesitis**

If enthesitis is present with any of the 4 sites (lateral epicondyle humerus L + R, proximal achilles L + R), the patient is counted as a patient with enthesitis.

### **Leeds Dactylitis Index (LDI)**

The LDI measures the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot: a minimum difference of 10% is used to define a dactylitic digit. If both sides are considered involved, a table of normative values is used to provide the comparison. The ratio of circumference is multiplied by a tenderness score, originally based on the Ritchie index (graded 0–3), but a later modification amended this to a binary score (0 for nontender, 1 for tender) — this later modification is referred to as the LDI basic, and is adopted in this study. For each dactylitic digit, the final score is:

$$[\{(A/B) - 1\} * 100] * C,$$

where A is circumference of involved digit, B circumference of opposite (unaffected or from reference) and C is tenderness (0 or 1 in this case). The results from each digit with dactylitis are then summed to produce a final score. Only involved digits are assessed.

### **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 patient is counted as a patient with dactylitis.

### Psoriasis Area and Severity Index (PASI)

The PASI assessment will be conducted for subjects in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at baseline (Visit 2). 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 will be derived as indicated in Table 11-3. 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:

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

**Table 11-3 The PASI scoring system**

<b>Body region</b>	<b>Erythema (E)</b>	<b>Thickening (plaque elevation, induration, I)</b>	<b>Scaling (desquamation) (D)</b>	<b>Area score (based on true area %, A)*</b>
Head (H)**	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%
Trunk, (T)***	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%
Upper limbs (U)	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%
Lower	0=none	0=none	0=none	0 = 0%

Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation) (D)	Area score (based on true area %, A)*
limbs (L)****	1=slight	1=slight	1=slight	1 = 1-9%
	2=moderate	2=moderate	2=moderate	2 = 10-29%
	3=severe	3=severe	3=severe	3 = 30-49%
	4=very severe	4=very severe	4=very severe	4 = 50-69%
				5 = 70-89%
				6 = 90-100%

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

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

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

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

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

$$\text{PASI} = 0.1(\text{E}_H + \text{I}_H + \text{D}_H)\text{A}_H + 0.2(\text{E}_U + \text{I}_U + \text{D}_U)\text{A}_U + 0.3(\text{E}_T + \text{I}_T + \text{D}_T)\text{A}_T + 0.4(\text{E}_L + \text{I}_L + \text{D}_L)\text{A}_L$$

The keys for the letters are provided in [Table 11-3](#).

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 total score comes from eCRF.

### IGA mod 2011

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

The IGA mod 2011 rating scale for overall psoriatic disease is displayed in [Table 11-4](#).

**Table 11-4 The IGA mod 2011 rating scale**

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

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

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

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

Based on this scale, subjects will be considered as **IGA mod 2011 0 or 1 responder** if they achieve a score of 0 or 1 and improve by at least 2 points on the IGA scale compared to baseline.

### **Target lesion score (TLS)**

The Target Lesion Score will be done for subjects enrolled in the study having a psoriatic target lesion that is at least 2 cm in diameter identified at baseline. At specified visits this target lesion will be scored for erythema, scaling, and thickness, each on a scale of 0 to 4 (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe). The parameter scores will be summed automatically in the eCRF, giving a score ranging from 0 to 12.

### **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. The mNAPSI scores range from 0-130 for all finger nails. The total mNAPSI score will be calculated as the sum of all the scores from available nails.

## **11.2 Description of Health-related Quality of Life Endpoints**

### **SF-36**

The Short Form Health Survey (SF-36) is a widely used and extensively studied instrument to measure health-related quality of life among healthy subjects and patients 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 patients. The eight domains are based on a scale from 0-100 while PCS and MCS are norm-based scores with a mean of 50 and a standard deviation of 10.

## **FACIT - Fatigue**

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue<sup>®</sup>) is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function.

Subjects respond to each item on a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much) based on their experience of fatigue during the past 2 weeks. The scale score is computed by summing the item scores, after reversing those items that are worded in the negative direction. Numbering the questions from 1 to 13, it is evident that questions 7 and 8 are worded in the positive direction (4 indicates a desirable response) and all other questions are worded in the negative directions (4 indicates an undesirable response). Thus, it is necessary to reverse the responses for questions 7 and 8 (i.e. original response of 0 gets mapped to 4, 1=3, 2=2, 3=1, and 4=0) for scoring purposes.

When there are missing item scores, the subscale score was computed by summing the non-missing item scores, multiplying by 13 (the total number of items in the scale) and dividing by the number of non-missing items (i.e. normalizing the results). The latter rule applied only when at least half of the items (seven or more) are non-missing.

FACT Fatigue subscale scores range from 0 to 52, where higher scores represent less fatigue (Cella D et al., 2004).

## **EuroQoL 5D (EQ-5D)**

The EQ-5D is a widely used, self-administered questionnaire designed to assess health status in adults. The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Subjects rate each of these items from "no problem," "some problem," or "extreme problem." A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is "today," and the questionnaire requires approximately 5 to 10 minutes to complete.

The EQ-5D contains six items designed to assess health status in terms of a single index value or health utility score. One of the strengths of the EQ-5D approach is that it allows "weighting" by the patient of particular health states and the generation of patient utilities. Published weights are available that allow for the creation of a single summary health utility score. Overall scores range from 0 to 1, with lower scores representing a higher level of dysfunction.

## **PsAQoL**

The PsA quality of life (PsAQoL) questionnaire contains 20 individual yes/no questions where the total score is determined by the number of questions that received a "yes" response. A higher score reflects a poorer quality of life.



The PsAQoL score will not be calculated if more than 4 questions are missing. Otherwise, divide the number of 'yes' by the number of answered questions, multiply by 20.

### **Dermatology Life Quality Index (DLQI)**

The Dermatology Life Quality Index (DLQI) is a 10-item general dermatology disability index designed to assess health-related quality of life in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral warts. The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 32 different skin conditions and is available in multiple languages. The recall period is the past week, and the instrument requires 1 to 2 minutes for completion.

Each item has four response categories ranging from 0 (not at all) to 3 (very much). "Not relevant" is also a valid response and is scored as 0. The DLQI total score is a sum of the 10 questions. Scores range from 0 to 30, and higher scores indicate greater health-related quality of life impairment. If two or more questions are left unanswered, the total score will not be calculated.

### **Work Productivity and Activity Impairment - General Health (WPAI-GH)**

The Work Productivity and Activity Impairment (WPAI-GH) questionnaire is an instrument to measure impairments in both paid work and unpaid work. It measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problem during the past seven days. The WPAI-GH consists of six questions:

- 1 = currently employed
- 2 = hours missed due to health problems
- 3 = hours missed other reasons
- 4 = hours actually worked
- 5 = degree health affected productivity while working (VAS)
- 6 = degree health affected productivity in regular unpaid activities (VAS)

The recall period for the questions 2 to 6 is seven days.

Four main outcomes can be generated from the WPAI-GH and expressed in percentages by multiplying the following scores by 100:

- 1) percent work time missed due to health =  $Q2/(Q2 + Q4)$  for those who were currently employed;
- 2) percent impairment while working due to health =  $Q5/10$  for those who were currently employed and actually worked in the past seven days;
- 3) percent overall work impairment due to health  $Q2/(Q2 + Q4) + ((1 - Q2/(Q2 + Q4)) \times (Q5/10))$  for those who were currently employed;
- 4) percent activity impairment due to health  $Q6/10$  for all respondents.

For those who missed work and did not actually work in the past seven days, the percent overall work impairment due to health will be equal to the percent work time missed due to health.

### **11.3 Handling of missing data**

#### **Missing data**

Missing data for ACR20 response and other binary efficacy variables for data up to 1-year (Week 52) 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 52.
- Subjects who do not have the required data to compute ACR20 response at baseline and at the specific time point will be classified as non-responders.

Patients who were unblinded prior to the scheduled timepoint will be considered non-responders from the time of unblinding up to the end of the placebo-controlled period (Week 24). The primary analysis will use the non-responder imputation.

Continuous variables (e.g. ACR20 components) will be analyzed using a mixed-effects repeated measures model (MMRM) which is valid under the missing at random (MAR) assumption. As such, single-point imputation of missing data will not be performed (e.g. LOCF). For analyses of these parameters, if all post-baseline 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.

#### **Data post-rescue**

In general, the handling of data for subjects who are rescued at Week 16 will be handled in the following fashion (up to Week 24):

- For binary endpoints, subjects will be considered non-responders. This will be done for all treatment regimens in order to minimize bias.
- For continuous endpoints, the goal of the analyses would be to estimate what would have happened if the patients had stayed on the original treatment. Thus, the data collected after the patient switches to secukinumab will be treated as missing for placebo patients and will be analyzed using a mixed-effects repeated measures model (MMRM) which is valid under the missing at random (MAR) assumption. For secukinumab patients, the actual values will be used in the analysis.

Data collected after Week 52 will generally be presented as ‘observed case’; i.e. all available data for each time point will be included in the analyses.

### **11.4 Analysis of Primary variable**

The primary efficacy variable will be ACR20 response at Week 24. The analysis of the primary efficacy variable will be based on the FAS. Primarily, CRP will be used instead of ESR to calculate ACR response; ESR will only be used in the event CRP is missing.

## Statistical analysis

The statistical hypothesis for ACR20 being tested is that there is no difference in the proportion of subjects fulfilling the ACR20 criteria at Week 24 in any of the secukinumab regimens versus placebo regimen.

Let  $p_j$  denote the proportion of ACR20 responders at Week 24 for treatment regimens  $j, j=0, 1, 2$ , where

- 0 corresponds to placebo regimen,
- 1 corresponds to secukinumab 75 mg s.c.,
- 2 corresponds to secukinumab 150 mg s.c.,

In statistical terms,  $H_j: p_j = p_0$ ,  $H_{Aj}: p_j \neq p_0$ , for the  $j^{\text{th}}$  secukinumab regimen, i.e.

$H_1$ : secukinumab 75 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24

$H_2$ : secukinumab 150 mg s.c. is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24

The primary endpoint of ACR20 at Week 24 will be analyzed via logistic regression with treatment and TNF-alpha inhibitor status as factors and weight as a covariate. Odds ratios will be computed for comparisons of secukinumab regimens versus placebo regimen utilizing the logistic regression model fitted.

For subjects meeting the criteria for early escape at Week 16, their ACR20 will be set to non-response at Week 24. This applies for all three treatment regimens in order to minimize bias.

## 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.

In order to determine the robustness of the logistic regression model used for the primary analysis, ACR20 response at Week 24 will also be evaluated using a non-parametric regression ([Koch et. al 1998](#)) model with the same independent variables as the logistic regression model. In addition, further logistic regression models may be conducted which explore the impact of other baseline or disease characteristics on response. Treatment by factor interactions will be explored.

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:

- Multiple imputation
- Observed data analysis

## 11.5 Analysis of secondary variables

The secondary efficacy variables include:

- response to treatment at Week 24 according to the PASI75 criteria in the subgroup of subjects who have  $\geq 3\%$  skin involvement
- response to treatment at Week 24 according to the PASI90 criteria in the subgroup of subjects who have  $\geq 3\%$  skin involvement
- change from baseline in DAS28-CRP at Week 24 in the FAS
- change in SF-36 PCS from baseline at Week 24 in the FAS
- change in HAQ-DI from baseline at Week 24 in the FAS
- response to treatment at Week 24 according to the ACR50 criteria in the FAS
- change from baseline in mTSS at Week 24 pooled secukinumab regimen vs placebo in the FAS
- presence of dactylitis at Week 24 pooled secukinumab regimen vs placebo in the subset of subjects who have dactylitis at baseline
- presence of enthesitis at Week 24 pooled secukinumab regimen vs placebo in the subset of subjects who have enthesitis at baseline
- change from baseline in mTSS at Week 24 individual secukinumab regimen vs placebo in the FAS

### **Testing strategy to control type I error**

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<sub>1</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to ACR20 response at Week 24

H<sub>2</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to ACR20 response at Week 24

Secondary objectives:

H<sub>3</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to PASI75 response at Week 24

H<sub>4</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to PASI75 response at Week 24

H<sub>5</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to PASI90 response at Week 24

H<sub>6</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to PASI90 response at Week 24

H<sub>7</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for DAS28-CRP at Week 24

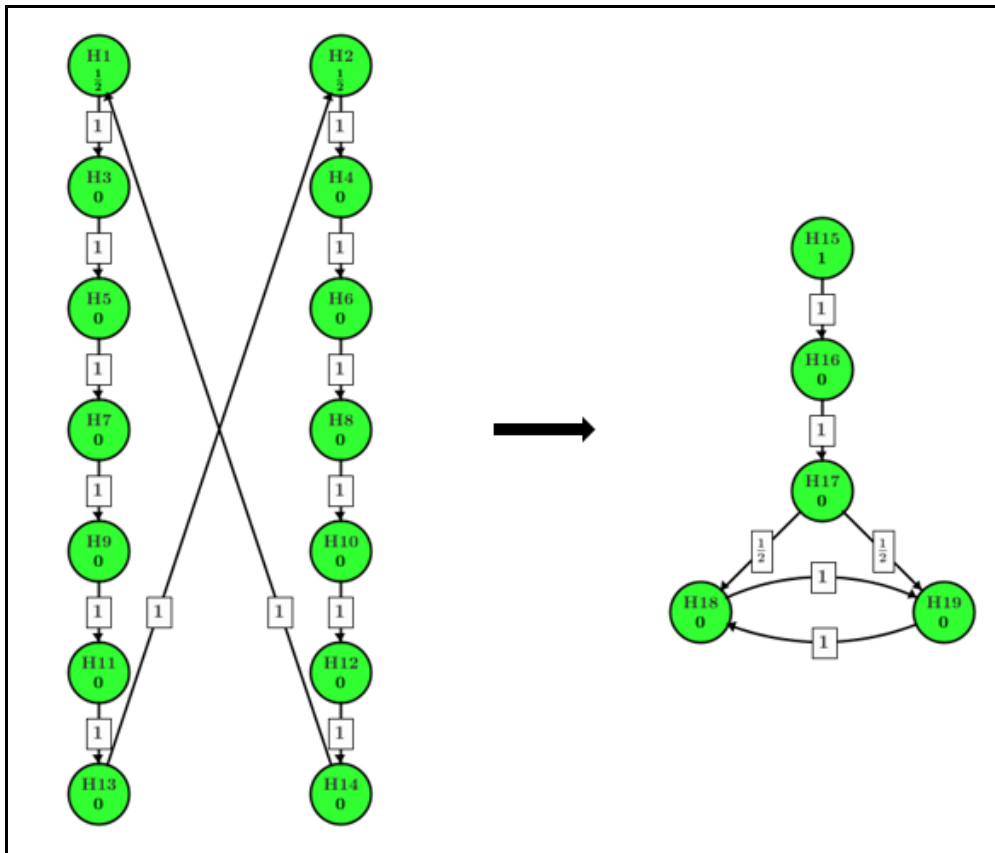
H<sub>8</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for DAS28-CRP at Week 24

H<sub>9</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for SF36-PCS at Week 24

- H<sub>10</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for SF36-PCS at Week 24
- H<sub>11</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at Week 24
- H<sub>12</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at Week 24
- H<sub>13</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to ACR50 response at Week 24
- H<sub>14</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to ACR50 response at Week 24
- H<sub>15</sub>: Secukinumab pooled regimen (75 mg and 150 mg s.c.) is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24
- H<sub>16</sub>: Secukinumab pooled regimen (75 mg and 150 mg s.c.) is not different to placebo regimen with respect to presence of dactylitis at Week 24
- H<sub>17</sub>: Secukinumab pooled regimen (75 mg and 150 mg s.c.) is not different to placebo regimen with respect to presence of enthesitis at Week 24
- H<sub>18</sub>: Secukinumab 75 mg s.c. is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24
- H<sub>19</sub>: Secukinumab 150 mg s.c. is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24

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

Figure 11-1 Testing strategy



The family-wise error will be set to  $\alpha=5\%$  and it will be controlled with the proposed hierarchical testing strategy. With this hierarchical testing approach, the hypotheses will be separated into two families, hypotheses of signs and symptoms ( $H_1 \sim H_{14}$ ) will be the first family and hypotheses of structure damage ( $H_{15} \sim H_{19}$ ) will be the second family. The second family hypotheses will be tested only when all hypotheses in the first family have been rejected. Each of the hypotheses ( $H_1$  and  $H_2$ ) for the primary objective (based on signs and symptoms at week 24) for each secukinumab regimen versus placebo will be tested simultaneously at  $\alpha/2$ . If at least one of  $H_1$  and/or  $H_2$  are/is rejected, then  $H_3$  and/or  $H_4$ , respectively. If at least one of  $H_3$  and/or  $H_4$  is rejected, the hypothesis  $H_5$  and/or  $H_6$ , is tested, respectively. Similar process applies until  $H_{13}$  and  $H_{14}$ . Once all hypotheses within the first family for a secukinumab regimen are rejected, then the respective  $\alpha/2$  can be passed on to the other regimen's hypotheses within the family, if they are not already rejected at  $\alpha/2$ . Only when all  $H_1 \sim H_{14}$  are rejected, the objective on joint structure endpoint at Week 24 for testing pooled secukinumab doses versus placebo ( $H_{15}$ ) will be tested at  $\alpha$ . If  $H_{15}$  is rejected, then  $H_{16}$  is tested at  $\alpha$ . Similarly if  $H_{16}$  is rejected, then  $H_{17}$  is tested at  $\alpha$ . If these pooled hypotheses are all rejected, then hypotheses concerning individual regimens of secukinumab versus placebo ( $H_{18}$  and  $H_{19}$ ) can be tested for a particular regimen at  $\alpha/2$ . Once the hypothesis of structure damage for a secukinumab regimen is rejected, then the respective  $\alpha/2$  can be passed on to the other regimen's hypothesis, if it is not already rejected at  $\alpha/2$ . Of note, in the description above, rejection of a hypothesis refers to rejection of the two-sided hypothesis; however the level of a rejected hypothesis is only passed on according to the graphical procedure for the test of another hypothesis if the treatment effect is in favor of secukinumab.

### **PASI 75 and PASI 90 response**

PASI 75 response and PASI 90 at Week 24 will be evaluated for those subjects in whom the assessment occurred (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.

### **Changes in DAS28-CRP**

Between-treatment differences in the change from baseline in DAS28-CRP will be compared by means of a mixed model repeated measures (MMRM) with treatment regimen, analysis visit, and TNF-alpha inhibitor status as factors, and weight and baseline as continuous covariates. Treatment by analysis visit and baseline 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 secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

## **SF-36 PCS**

Between-treatment differences in the change in SF-36 PCS will be evaluated using a mixed effect repeated measures model (MMRM). Treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline SF-36 score and weight as continuous covariates. Treatment by analysis visit and baseline 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.

## **Physical function (HAQ-DI)**

Between-treatment differences in the change in HAQ-DI 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 baseline HAQ-DI score as continuous covariates. Treatment by analysis visit and baseline 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 secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

## **ACR50 at Week 24**

Response at Week 24 to ACR50 in the FAS will be evaluated using a logistic regression model with treatment and randomization stratum (TNF $\alpha$  status -naive or IR) as factors and weight as a covariate.

## **Joint/bone structural damage at Week 24**

The change at Week 24 from baseline van der Heijde total modified Sharp score will be evaluated using a non-parametric ANCOVA model with treatment regimen and TNF-alpha inhibitor status as factors, and weight and baseline van der Heijde total modified Sharp score as covariates. The pooled secukinumab regimens (75 mg s.c. and 150 mg s.c.) will be compared to placebo, then each of the secukinumab regimens will be compared versus the placebo regimen via pairwise comparisons.

For subjects who meet the criteria for early escape at Week 16 and subjects who discontinue the study prior to Week 24, linear extrapolation will be used to impute the value at Week 24. In order to minimize bias, the extrapolation will use baseline and all post-baseline data up to the point the subject meets criteria for early escape treatment, or discontinues the study. If baseline or all post-baseline total modified Sharp score/s is/are missing for a subject, the subject will be excluded from the analyses.

The primary analysis of joint/bone structural damage will define baseline as the last measurement prior to dosing if available, or the first value within 30 days post dosing if no value available prior to dosing. A sensitivity analysis will be performed excluding patients whose baseline measure is after Day 1.

## **Dactylitis at Week 24**



Presence of dactylitis at Week 24 in the subset of subjects who have dactylitis at baseline will be evaluated using a logistic regression model with treatment and randomization stratum (TNF $\alpha$  status -naive or IR) as factors and weight as a covariate.

### **Enthesitis at Week 24**

Presence of enthesitis at Week 24 in the subset of subjects who have enthesitis at baseline will be evaluated using a logistic regression model with treatment and randomization stratum (TNF $\alpha$  status -naive or IR) as factors and weight as a covariate.

## **11.6 Analysis of exploratory variables**

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

- HAQ-DI response
- Major clinical response by Week 52 and 104
- Joint/bone structural damage at Week 52 and 104
- Evidence of no disease progression at Week 24, 52 and 104
- PsARC, ACR20/50/70 response over time
- DAS28 remission, low disease activity, EULAR response at Week 24 and over time
- Minimal disease activity
- ACR components
  - Changes in tender joint counts over time
  - Change in swollen joint counts over time
  - Change in Patient's global assessment in disease activity
  - Change in Physician's global assessment in disease activity
  - Change in PsA Pain
  - Change in HAQ-DI over time
  - Change in erythrocyte sedimentation rate (ESR)
  - Change in high-sensitivity C-reactive protein (hsCRP)
- PASI 75, PASI 90, and IGA response over time
- Target lesion score
- mNAPSI
- LDI and dactylitis count
- LEI-4

Between-treatment comparisons for binary variables in the FAS population (e.g PsARC, ACR20, etc.) at individual analysis visits will be evaluated using a logistic regression model with treatment and TNF-alpha inhibitor status as factors and baseline score (if appropriate) and weight as covariates.

Continuous variables (e.g. change from baseline in PsA pain) will be evaluated using a mixed-effect model repeated measures (MMRM) with treatment regimen, TNF-alpha inhibitor status, and analysis visit as factors and weight and baseline score as continuous covariates. Treatment by analysis visit and baseline 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 secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits. Variables such as hsCRP whose distribution is not anticipated to be normal will be transformed and analyzed on the log<sub>e</sub> scale.

### **Joint/bone structural damage at Week 52 and 104**

The change in joint/bone structural damage from baseline to Week 52 will be evaluated using evaluable data similarly to the analysis for Week 24. The pooled secukinumab regimens (75 mg s.c. and 150 mg s.c.) will be compared to placebo, then each of the secukinumab regimens will be compared versus the placebo regimen via pairwise comparisons.

As sensitivity analysis, for subjects with missing modified Sharp score values at Week 52, their Week 52 value will be imputed by linear extrapolation from baseline, Week 16 and Week 24, and at subject discontinuation visit (if subject discontinued prior to Week 52) to Week 52.

Summary statistics of evaluable data at Week 52 will be provided for each treatment regimens: secukinumab 75 mg, secukinumab 150 mg, placebo escape or switch to secukinumab 75 mg at Week 16 or 24, placebo escape or switch to secukinumab 150 mg at Week 16 or 24. Summary statistics include mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum.

Evaluable Joint/bone structure data at Week 104 will be summarized by treatment group. In addition, the change from week 52 will also be summarized within treatment regimen.

### **Evidence of no disease progression at Week 24, 52 and 104**

The proportion of subjects without disease progression will be defined as those subjects who have a change in van der Heijde total modified Sharp score at Week 24 relative to baseline  $\leq 0$ . The proportion of subjects without disease progression at Week 24 will be evaluated using a logistic regression model with treatment group and randomization strata, as factors, weight and baseline van der Heijde total modified Sharp score as covariates.

The proportion of subjects without disease progression at Week 52 and 104 will be evaluated in the same manner. At week 104, the proportion of subjects with disease progression from week 52 will also be examined.

## **EULAR response at Week 24 and over time**

Based on the EULAR response criteria (good responder, moderate responder, and non-responder) as determined based on the value of DAS28-CRP achieved and the magnitude of change from baseline, between-treatment differences in EULAR response at Week 24 and other analysis visits will be evaluated using a proportional odds regression model with treatment group and randomization strata as factors and weight and baseline DAS28-CRP score as covariates. Frequency tables will also be presented to show the response rate over time up to Week 24 and Week 52, as appropriate.

## **Magnetic Resonance Imaging**

MRI Analysis will be based on the patients who have MRI performed at selected centers.

The change in synovitis between Week 24 and baseline will be evaluated using a nonparametric ANCOVA model with treatment regimen as a factor, weight and baseline as covariates. Pair-wise comparison versus placebo will be made for each of the secukinumab regimens. Tenosynovitis, periarticular inflammation, bone edema/osteitis, bone erosion, bone proliferation, and joint space narrowing will be evaluated in the same manner.

For subjects with missing data at Week 24, linear extrapolation will be used to impute missing data. In order to minimize bias, the extrapolation will use baseline and week 12. Change from baseline will be summarized by analysis visit with summary statistics including mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum.

### **LEI-4**

The 4-site LEI (i.e. score with the four correct sites: lateral epicondyle humerus L + R and proximal achilles L + R) will be summarized by treatment group and visit. Change from baseline in the 4-site LEI will be analyzed using a nonparametric ANCOVA model with treatment regimen and randomization strata as factors, weight and baseline score as covariates. Pair-wise comparison versus placebo will be made for each of the secukinumab regimens by visit.

## **11.7 Analysis of Health-related Quality of life variables**

### **PsAQoL**

Between-treatment differences in the change from baseline for PsAQoL scores will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline and weight as continuous covariates. Treatment by analysis visit and baseline 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.

## **SF-36**

The following variables will be evaluated:

- SF-36 domain scores (based on a scale of 0-100).
- SF-36 PCS and MCS scores (norm-based scores).
- SF-36 PCS responder (improvement of  $\geq 2.5$  points, [Lubeck 2004](#))

Between-treatment differences in the change from baseline for SF-36 summary scores (PCS/MCS) will be evaluated using a mixed effect repeated measures model (MMRM). Treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline SF-36 score and weight as continuous covariates. Treatment by analysis visit and baseline 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.

In the responder analyses, treatment groups will be compared with respect to response to treatment using a logistic regression model with treatment and TNF-alpha inhibitor status as factors, baseline SF-36 summary score and weight as covariates. Odds ratios with corresponding 95% confidence intervals will be estimated in addition.

Individual SF-36 domain scores will be summarized.

## **FACIT-Fatigue**

Between-treatment differences in the change from baseline for FACIT-Fatigue scores will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline and weight as continuous covariates. Treatment by analysis visit and baseline 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.

## **EuroQol 5D (EQ-5D)**

The number and percentage of subjects in each of the three categories for each question will be presented by visit and treatment group.

Summary statistics will be shown for the health state assessment by visit and treatment group.

For the change in EQ-5D overall health state (VAS), between-treatment differences in the change in EQ-5D overall health state (VAS) will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline EQ-5D overall health state (VAS) and weight as continuous covariates. Treatment by analysis visit and baseline EQ-5D overall health state (VAS) 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.

### **Dermatology Life Quality Index (DLQI)**

Between-treatment differences in the change from baseline for DLQI will be evaluated using a mixed effect repeated measures model (MMRM) with treatment group, analysis visit and TNF-alpha inhibitor status as factors and baseline and weight as continuous covariates. Treatment by analysis visit and baseline 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.

### **WPAI-GH**

Summary statistics will be shown for the WPAI-GH assessment by visit and treatment group.

## **12 Pharmacokinetic evaluations (change / add PD, PK/PD, Biomarkers, as needed)**

### **12.1 Pharmacokinetics**

All completed subjects with quantifiable pharmacokinetic (PK) measurements of secukinumab will be included in the pharmacokinetic data analysis. Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification as well as missing data will be labeled as such in the concentration data listings. PK concentrations will be summarized by visit and treatment group. In addition to mean, standard deviation (SD), coefficient of variation (CV), median and quartiles, the geometric mean and geometric coefficient of variation (CV) and n(log) will be presented. The formula for deriving the geometric mean and CV (%) is as following:

- $CV (\%) = (SD/mean)*100$ ,
- $geometric\ mean = \exp( (\text{sum of log transformed data}) / \text{number of non-missing data points after log transformation} )$ ,
- $geometric\ CV = \sqrt{ \exp( \text{variance of log-transformed data} ) - 1 } * 100$ .

In addition, sample number, concentration, sample date, sample time at pre-dose and minutes pre-dose will be listed by treatment sequence.

Values below lower limit of quantification/below detection limit will be imputed by 0.

Pharmacokinetic data of the study treatment will be analyzed with a population-pharmacokinetic mixed effects model. The analysis will be based on a pooled data set, including pharmacokinetic samples from previous studies. The modeling approach will be further detailed in a modeling plan. Results will be reported separately.

## **12.2 Pharmacogenetics**

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations will be evaluated with exploratory analyses. A range of statistical tests (chi-square tests, analysis of covariance (ANCOVA), linear and logistic regression) will be used for the analyses. Additional data, from subsequent clinical trials, are often needed to confirm associations. Alternatively, if the numbers of subjects enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

Results will be reported separately.

## **12.3 Biomarkers**

Soluble marker panel studies investigate differences in the level of expression of proteins or peptides between individuals in a given biofluid. The goal of such studies is to allow the identification of potential protein or peptide biomarkers of drug action or disease, and to better understand the associated underlying molecular mechanisms. By applying statistical analysis methods (e.g. principal component analysis) between subject groups, distinct study time points, or between study groups from other clinical trials, it may be possible to identify patterns which are associated with disease state or response to drug treatment. However, the exact type of data analysis method will depend on the type of data obtained in the study and thus the analysis of this data will be data driven.

Results will be reported separately.

## **12.4 PK/PD**

Exploratory analysis to investigate the correlation between the PK data and efficacy outcomes will be performed.

An indirect response model, driven by study treatment concentration, will be used to characterize the time course of efficacy response. Further details of the modeling approach will be specified in a modeling plan. Results will be reported separately.

## **13 Safety evaluation**

Summaries may be performed separately for initial (Week 1-16) and entire treatment periods. Week 16 is chosen due to the fact that placebo patients may be rescued as early as week 16. Use of data up to and including the last visit before rescue provides an unbiased comparison between AIN and placebo; data collected beyond week 16 are included in analyses which summarize the entire treatment period. The analyses of the follow-up period will be limited to summaries for treatment-emergent adverse events, serious adverse events and risks based on adverse events.

Safety analyses will be performed on treatment received or actual treatment as described below:

The actual treatment or treatment received for summaries of safety data will differ to the treatment assigned at randomization only if a subject received the wrong treatment during the entire study.

For those subjects who received not the treatment randomized, i.e. who received erroneously the wrong treatment at least once, an additional AE listing will be prepared displaying which events occurred after the treatment errors.

### **13.1 Adverse events**

The crude incidence of treatment emergent adverse events (i.e. events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized by primary system organ class and preferred term. Confidence intervals for the crude rate will be derived as described in [Section 18.2.4.1](#). In addition, exposure time-adjusted rates (incidence rate) including 95% confidence intervals will be provided for the entire treatment period (see [Section 18.2.5.1](#)) to adjust for differences in exposure. Graphical displays of the crude incidence rates and exposure-adjusted rates will be presented for all AEs and serious AEs by system organ class.

Adverse events reported will be presented in descending frequency according to its incidence in total secukinumab group (combining all secukinumab treatment groups) starting from the most common event. Summaries (crude incidences only) will also be presented for AEs by severity and for study treatment related AEs. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event 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.

Separate summaries will be provided for adverse events suspected to be related to study drug, deaths, serious adverse events, and adverse events leading to discontinuation and adverse events requiring concomitant medication.

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

Follow-up period summaries will be done for all subjects in follow-up who do not go on to the extension study (completers and early discontinuations).

A listing of non-treatment emergent adverse events will be done. These adverse events occurred before the first dose of the study treatment. The crude incidence rate will be provided without treatment information.

Algorithms for date imputations will be provided in RAP M8.

For SAEs occurred during screening a listing will be prepared for all subjects screened including screening failures.

An overview of the safety analyses and which will be performed for each analysis period is described in [Table 13-1](#).

**Table 13-1 Overview of analyses on some safety endpoints**

Analysis period	AEs & SAEs	AEs by severity	Study drug related AEs	AEs-SMQ	Risk	Notables for (vitals/ ECG), lab criteria
Day 1 – Week 16	•crude incidence	•crude incidence	•crude incidence	•crude incidence	•crude incidence	•crude incidence
Day 1 – Week 24	•exposure time adjusted incidence*					
Entire Treatment (up to week 104)	•crude incidence •exposure time adjusted incidence*	•crude incidence	•crude incidence	•exposure time adjusted incidence	•crude incidence •exposure time adjusted incidence	•crude incidence
follow-up (week 104 to 112)	•crude incidence				•crude incidence	

\*Exposure-adjusted incidence rates will be done at the PSOC for AE and SAE and Level 1 for Risks and SMQ analyses

## 13.2 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, chemistry and urinalysis). In addition to the individual laboratory parameters the ratios “total cholesterol / HDL” and “apolipoprotein B / apolipoprotein A1” will be derived and summarized.

For urinalysis, frequency tables will be presented.

Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values and will be calculated as:

$$\text{change from baseline} = \text{post baseline value} - \text{baseline value}$$



For each parameter, the maximum change (maximum decrease and maximum increase) from baseline, if appropriate for each study phase, will be analyzed analogously.

In addition, shift tables will be provided for all parameters to compare a subject’s baseline laboratory evaluation relative to the visit’s observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. If appropriate, the shifts to the most extreme laboratory test value within a treatment phase (either initial or entire) will be presented as well (including category “high and low”). These summaries will be presented by laboratory test and treatment group.

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in [Table 13-2](#): hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose, cholesterol, triglycerides (TG).

These summaries will be split into hematology and chemistry for study level reports and the pooled summary of clinical safety.

**Table 13-2 CTCAE grades for laboratory parameters to be analyzed**

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	
Platelet count decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased*	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
TBL increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Glucose increased (Hyperglycemia )	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Glucose decreased (Hypoglycemia)	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L
Cholesterol high	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
Hypertriglyceridemia	1.71 - 3.42 mmol/L	>3.42 - 5.7mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L

\*Note: for “creatinine increased” the baseline criteria do not apply

Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment phase (either initial or entire) analyzed. Of note, baseline will be defined as last assessment prior to first dosing in initial treatment phase. Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

Summaries for newly occurring or worsening clinically notable lipid abnormalities will also be provided cumulatively for each of the following parameters and categories:

- HDL:
  - $\leq$ LLN
  - $<0.8 \times$  LLN
- LDL, cholesterol, triglycerides:
  - $\geq$ ULN
  - $>1.5 \times$  ULN
  - $>2.5 \times$  ULN

Newly occurring or worsening liver enzyme abnormalities will also be summarized based on the event criteria given in [Table 13-3](#):

**Table 13-3 Liver-related events**

Parameter	Criterion
ALT	$>3xULN$ ; $>5xULN$ ; $>8xULN$ ; $>10xULN$ , $>20xULN$
AST	$>3xULN$ ; $>5xULN$ ; $>8xULN$ $>10xULN$ ; $>20xULN$
ALT or AST	$>3xULN$ ; $>5xULN$ ; $>8xULN$ $>10xULN$ ; $>20xULN$
TBL	$>1.5xULN$ , $>2xULN$ , $>3xULN$ ,
ALP	$>2xULN$ , $>3xULN$ . $>5xULN$
ALT or AST & TBL	ALT or AST $>3xULN$ & TBL $>2xULN$ ; ALT or AST $>5xULN$ & TBL $>2xULN$ ; ALT or AST $>8xULN$ & TBL $>2xULN$ ; ALT or AST $>10xULN$ & TBL $>2xULN$
ALP & TBL	ALP $>3xULN$ & TBL $>2xULN$ ALP $>5xULN$ & TBL $>2xULN$
ALT or AST & TBL & ALP	ALT or AST $>3xULN$ & TBL $>2xULN$ & ALP $<2xULN$ ( <b>Hy's Law</b> ) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of <i>pure hepatocellular injury</i> . This does not mean that cases of ALT or AST $>3xULN$ & TBL $>2xULN$ & ALP $\geq 2xULN$ may not result in severe DILI.

Notes:

1) In studies which enroll subjects with pre-existing liver disease, baseline LFT may be increased above ULN; in such a case it is meaningful to add the condition "and worse than baseline" to the abnormality criteria

For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same visit. The criteria are not mutually exclusive, e.g. a subject with ALT = 6.42xULN is counted for ALT  $>3xULN$  and ALT  $>5xULN$ .

Individual subject data listings will be provided for subjects with abnormal laboratory data. Data of subjects with newly occurring or worsening liver enzyme abnormalities will be listed in an additional listing.

Box plots over time will be presented for selected laboratory parameters (neutrophils, liver and lipid parameters).

### 13.3 Vital signs

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

$$\text{change from baseline} = \text{post-baseline value} - \text{baseline value}$$

The number and percentage of subjects with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in [Table 13-4](#) below.

**Table 13-4 Criteria for notable vital sign abnormalities**

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

### 13.4 Electrocardiogram (ECG)

The following quantitative variables will be summarized: ventricular rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc). Both Bazett (QTcB) and Fridericia (QTcF) corrections will be presented for QTc.

QTc will be summarized by computing the number and percentage of subjects (including 95% confidence intervals for pooled analyses, e.g. DMC or SCS) with:

- QTc  $> 500$  msec
- QTc  $> 480$  msec
- QTc  $> 450$  msec
- QTc changes from baseline  $> 30$  msec
- QTc changes from baseline  $> 60$  msec
- PR  $> 250$  msec

Summary statistics will be presented for ECG variables by visit and treatment group.

In addition, shift tables comparing baseline ECG interpretation (normal, abnormal, not available, total) with the worst on-study interpretation (normal, abnormal, not available, total) will be provided.

A listing of all newly occurring or worsening abnormalities will be provided, as well as a by-subject listing of all quantitative ECG parameters.

### 13.5 Immunogenicity

A listing of immunogenicity (anti-AIN457 antibodies) will be provided.

### **13.6 Compound specific safety evaluation**

Safety topics of interest, such as risks defined in the Safety Profiling Plan, Risk Management Plan or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet that is stored in CREDI at the path Cabinets/CREDI Projects/A/AIN457A/Integrated Medical Safety.

The crude incidence and exposure-adjusted incidence rates for potential compound and class-related risks and routine risks will be summarized. In addition, listings will be provided presenting which subjects experienced which risk.

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

## **14 Sample size calculation**

The original power calculations used in the protocol have been updated to incorporate more recent published data in the PsA population. In addition, the statistical hierarchy (primary plus ranked secondary variables) was expanded to include more endpoints important in the treatment of psoriatic arthritis patients. No adjustment was made to the sample size as a result of the updated power calculations; the original sample size of N=200 per treatment regimen was retained. The adjustments to the power calculations and the statistical hierarchy were done before the unblinding of the trial in order to prevent bias.

A 5% two-sided type I error rate will be used to control for type I error. Two secukinumab doses will be tested versus placebo with respect to the primary endpoint (ACR20 response at Week 24), thus the type-I-error will be split to 2.5% two-sided for each comparison. Sample sizes will be based on this type I error assumption.

A placebo response rate of about 25% after 24 weeks was reported for the TNF $\alpha$  inhibitor naïve population in the PSUMMIT I study ([McInnes et al 2013](#)), and 15% was reported for the TNF $\alpha$  inhibitor IR population in the PSUMMIT II study ([Ritchlin et al 2013](#)). Based on the weighted average, the overall placebo rate is expected to be 22%.

The response on secukinumab is expected to be 55% in the TNF $\alpha$  inhibitor naïve population and 35% in the TNF $\alpha$  inhibitor IR-population. Based on the weighted average, the overall rate on a dose of secukinumab is expected to be 49%.

For the primary endpoint, ACR20 in the overall population, 200 subjects per group would yield approximately 99% power to detect a treatment difference of 27% (Fisher's exact test, nQuery 7.0).

## **15 Power for analysis of secondary variables**

Power for secondary variables was calculated using a two-sided 2.5% type I error. With an assumed placebo rate of 7.6% and secukinumab 58.1%, the study is over 99% powered to detect a treatment difference of PASI75 in the full FAS population, assuming 135 subjects per treatment arm (Fisher's exact test, nQuery 7.0). Similarly, with an assumed placebo rate of 5% and secukinumab 44%, the study is over 99% powered to detect a treatment difference of PASI90 in the full FAS population, assuming 135 subjects per treatment arm. It is assumed that about 67.5% of enrolled patients have  $\geq 3\%$  skin involvement. Assumptions of PASI75 and PASI90 rates are based on PSUMMIT I and II studies (McInnes et al 2013 and Ritchlin et al 2013).

A difference of 1.31 and standard deviation of 1.34 has been observed for the change from baseline in DAS28-CRP in Golimumab (Kavanaugh et al 2009) for the TNF $\alpha$  inhibitor naïve population. Assuming the difference is half in the TNF $\alpha$  inhibitor IR population, the overall population has a difference of 1.12. With these assumptions, the study has approximately over 99% power to detect a difference between secukinumab and placebo (Two group t-test, nQuery Advisor 7.0), assuming 200 subjects per arm.

A standard deviation of approximately 10.1 and a treatment difference of 6.32 has been observed for the change from baseline at week 24 in SF36-PCS in Ustekinumab trial (McInnes et al 2013). Using those assumptions, the study has approximately 99% power to detect a difference between secukinumab and placebo (Two group t-test, NQuery Advisor 7.0), assuming 200 subjects per arm.

A standard deviation of approximately 0.5 and a treatment difference of 0.25 has been observed for the change from baseline at week 24 in HAQ-DI in Ustekinumab trial (McInnes et al 2013; Ritchlin et al 2012; Ritchlin et al 2013). Using those assumptions, the study has approximately 99% power to detect a difference between secukinumab and placebo (Two group t-test, NQuery Advisor 7.0), assuming 200 subjects per arm.

With an assumed placebo rate of 7.4% (McInnes et al 2013 and Ritchlin et al 2013) and secukinumab 25.5%, the study is over 99% powered to detect a treatment difference of ACR50 in the full FAS population, assuming 200 subjects per treatment arm (Fisher's exact test, nQuery 7.0).

For structural endpoint, historical data (adalimumab) showed a standard deviation of 1.2 on active treatment and 2.4 on placebo at week 26, and a difference of 0.6 for the TNF $\alpha$  inhibitor naïve population. Assuming the difference is half in the TNF $\alpha$  inhibitor IR population, the overall population has a difference of 0.51. Using the above assumptions, there is 80% power to show statistically significant differences between secukinumab (pooled 400 subjects) and placebo (200 subjects). Individual comparisons between secukinumab and placebo would have 66% power (Satterthwaite t-test, nQuery 7.0).

For the presence of dactylitis at Week 24 in the subset of patients who have dactylitis at baseline, with an assumed placebo rate of 76% (McInnes et al 2013) and secukinumab 57%, there is about 89% power to show statistically significant difference between secukinumab (pooled 200 subjects) and placebo (100 subjects), assuming 50% patients have dactylitis at baseline (Fisher's exact test, nQuery 7.0).

For the presence of enthesitis at Week 24 in the subset of patients who have enthesitis at baseline, with an assumed placebo rate of 81% (McInnes et al 2013) and secukinumab 65%, there is about 87% power to show statistically significant difference between secukinumab (pooled 240 subjects) and placebo (120 subjects), assuming 60% patients have enthesitis at baseline (Fisher's exact test, nQuery 7.0).

## **16 Interim Analysis**

The Week 52 analysis will be performed after all subjects have completed the Week 52 visit. For this analysis, all subjects will have completed the assessments related to the primary and secondary objectives. Thus, no adjustment will be made to the type I error rate for this analysis and an interim clinical study report will be produced.

## **17 DMC**

A project-level DMC will monitor the trials' progress for unexpectedly large differences in toxicity between treatment groups on a regular basis or per the request of the DMC. Details regarding the reasons for the DMC and the grounds for stopping/continuing studies, as well as the DMC procedures are provided in the project-level DMC charter.

## **18 Appendix**

### **18.1 Visit Windows**

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

Of note, subjects are allowed to have gaps in visits. All data collected will be displayed in listings.

**Table 18-1 Analysis visit windows**

Analysis Visit	Target Day	Analysis Visit Window	Group1	Group2	Group3	Group4	Group5	Group6	Group7	Group8	Group9	Group10	Group11
Baseline	1	Up to 1*	Up to 1*	Up to 1*	Up to 7	Up to 1*	Up to 1*	Up to 1*	Up to 1*	Up to 1*	Up to 1*	Up to 1*	Up to 30
Week 1	8	2-11	2-11	2-11					2-11				
Week 2	15	12-22	12-22	12-22				2-22	12-22				
Week 4	29	23-43	23-43	23-43			2-71	23-43	23-43	2-43			
Week 8	57	44-71	44-71	44-71				44-71	44-71	44-71	2-85		
Week 12	85	72-99	72-99	72-99	8-127			72-99	72-99	72-99			
Week 16	113	100-127	100-127	100-127		2-141	72-141	100-141	100-141	100-141	86-141	2-239	31-141
Week 20	141	128-155	128-155	128-155									
Week 24	169	156-183	156-183	156-183	128-449	142-267	142-267	142-197	142-197	142-267	142-267		142-267
Week 28	197	184-211	184-211	184-211									
Week 32	225	212-239	212-239	212-253				198-253	198-253				
Week 36	253	240-267	240-267										
Week 40	281	268-295	268-295	254-323				254-323	254-323				
Week 44	309	296-323	296-323										
Week 48	337	324-351	324-351										
Week 52	365	352-379	352-393	324-393		268-547	268-547	324-393	324-393	268-547	268-449	240-547	268-547
Week 56	393	380-407											
Week 60	421	408-435	394-449	394-449				394-449	394-449				
Week 64	449	436-463											
Week 68	477	464-491	450-505	450-505				450-505	450-505				
Week 72	505	492-519											
Week 76	533	520-547	506-561	506-561				506-561	506-561		450-631		



Week 80	561	548-575											
Week 84	589	576-603	562-617	562-617				562-617	562-617				
Week 88	617	604-631											
Week 92	645	632-659	618-687	618-687				618-687	618-687				
Week 96	673	660-687											
Week 100	701	688-715											
Week 104	729	716-743	688-743	688-743	450-743	548-743	548-743	688-743	688-743	548-743	632-743	548-743	548-743
<p>Group1: ACR components, Vital signs  Group2: Hematology, blood chemistry, urinalysis  Group3: MRI  Group4: WPAI-GH  Group5: PK  Group6: Presence of enthesitis, LEI, presence of dactylitis, LDI, dactylitis count  Group7: PASI, IGA, TLS, mNAPSI  Group8: SF-36, FACIT, PsAQoL, EQ-5D, DLQI  Group9: Lipids  Group10: ECG  Group11: X-ray</p> <p>* The first administration of randomized study treatment (first dose) is defined as 1.</p>													

The following rules are used to determine the window for an applicable visit post baseline: “Lower limit” = “upper limit of prior applicable visit” + 1. “Upper limit” = “target day of current visit” + integer part of (“target day of next applicable visit” – “target day of current visit”)/2. Lower limit of the first applicable visit is always Day 2.

The mapping described above applies to all visits (not just scheduled visits). Repeat and/or unscheduled visits (which will be numbered in the database according to new NCDS standards) will be mapped for analysis purposes in the same way as scheduled visits. This leaves the possibility, then, for multiple measurements within an analysis window. The following conventions will be used to determine the appropriate measurement to be summarized in the event of multiple measurements within a visit window.

**Table 18-2 Rules for flagging variables**

Timing of measurement	Type of data	Rule
Baseline	All data	The last measurement made prior to administration of the first dose of study treatment – note this may include measurements taken on the day of randomization (e.g. lab). If a patient did not receive any dose of study treatment then the randomization date will be used.
Post-baseline efficacy	All data	<ul style="list-style-type: none"> <li>• For visits without switch of treatment in the window, the measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g. 1 before target date and 1 after) the first one will be used.</li> <li>• For visits during which the patient switches from placebo to AIN the following will be done based on whether or not the patient met the rescue criteria:               <ul style="list-style-type: none"> <li>○ If the analysis visit window is &lt;= week 16(for non-responders) or week 24 (for responders), then:                   <ul style="list-style-type: none"> <li>▪ If available, the closest measurement to the target date which is ON or BEFORE the switch date will be used (i.e. the closest measurement to target which is on placebo).</li> <li>▪ If there are no data on or before the switch then the closest measurement to the target date after the switch will be used.</li> </ul> </li> <li>○ If the analysis visit window is &gt; week 16(for non-responders) or week 24 (for responders), then                   <ul style="list-style-type: none"> <li>▪ If available, the closest measurement to the target date which is AFTER the switch date will be used (i.e. the closest measurement to target which is on AIN).</li> <li>▪ If there are no data AFTER the switch then the closest measurement to the target date before the switch will be used.</li> </ul> </li> </ul> </li> </ul>
Post-baseline safety	Summary visit information (e.g. lab, ECG, etc.)	<ul style="list-style-type: none"> <li>• For visits without switch of treatment in the window, the measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g. 1 before target date and 1 after) the first one will be used.</li> <li>• For visits during which the patient switches from placebo to AIN the following will be done based on whether or not the patient met the rescue criteria:               <ul style="list-style-type: none"> <li>○ If the analysis visit window is &lt;= week 16(for non-responders) or week 24 (for responders), then:                   <ul style="list-style-type: none"> <li>▪ If available, the closest measurement to the target date which is ON or BEFORE the switch date will be used (i.e. the closest measurement to target which is on placebo).</li> <li>▪ If there are no data on or before the switch then the closest measurement to the target date after the switch will be used.</li> </ul> </li> </ul> </li> </ul>

Timing of measurement	Type of data	Rule
		<ul style="list-style-type: none"> <li>○ If the analysis visit window is &gt; week 16(for non-responders) or week 24 (for responders), then <ul style="list-style-type: none"> <li>▪ If available, the closest measurement to the target date which is AFTER the switch date will be used (i.e. the closest measurement to target which is on AIN).</li> <li>▪ If there are no data AFTER the switch then the closest measurement to the target date before the switch will be used.</li> </ul> </li> </ul>
Post-baseline safety	Notable abnormalities (e.g. lab)	The most extreme measurement in the window will be used. Note this means a patient can have a notably high and notably low measurement within a window.

## 18.2 Statistical methodology and assumptions

### 18.2.1 Analysis of continuous data

#### 18.2.1.1 Summary statistics for continuous data

Summary statistics (including N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum) will be provided for continuous data by visit and treatment group.

#### 18.2.1.2 Mixed-effects repeated measures model

Endpoints with continuous data type expected to be normally distributed (e.g. DAS28) will be analyzed using a mixed-effects repeated measures model (MMRM) with treatment, stratification factor and analysis visit as factors; and weight, baseline value, treatment by visit and baseline by visit interactions as covariates. An unstructured covariance structure will be assumed for this 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.

SAS code for mixed model:

```
proc mixed data=aaa;
```

```
class TRT USUBJID AVISITN STRATA;
```

```
model CHG=TRT STRATA AVISITN WEIGHT BASE TRT*AVISITN BASE*AVISITN  
/ s ddfm=kr;
```

```
lsmeans TRT*AVISITN / diff cl;
```

```
repeated AVISITN / type=un subject=USUBJID;
```

```
Run;
```

In case the MMRM model does not converge the following sequential steps will be used:

1. change ddfm=kr to ddfm=bw. If still no convergence, perform step 2.
2. change type=un to type=cs. If still no convergence, perform step 3.
3. remove covariates in the following order until convergence: WEIGHT, BASE\*AVISITN, STRATA.

### 18.2.1.3 Non-parametric analysis of covariance

A non-parametric ANCOVA model (Koch 1998) will be used for the endpoints that are not normally distributed, e.g. X-ray, MRI, et. ctrl. The macro NParCov3 will be used, see Zink and Koch 2012.

- For continuous response variable, the macro call will be as follows:

%NParCov3(OUTCOMES = response, COVARs = weight baseline, C=1,

HYPOTH = ALT, STRATA = TNF $\alpha$  status, TRTGRPS = treatment, TRANSFORM = NONE, COMBINE = FIRST, DSNIN = RESP, DSNOUT = OUTDAT);

Data set \_OUTDAT\_DEPTEST provides results for the treatment difference, and \_OUTDAT\_CI provides a 95% confidence interval for the treatment estimate.

- For binary response variable, the macro call will be as follows:

%NParCov3(OUTCOMES = response, COVARs = weight, C = 1, HYPOTH = ALT, STRATA = TNF $\alpha$  status, TRTGRPS = treatment, TRANSFORM = LOGISTIC,

COMBINE = FIRST, DSNIN = RESP, DSNOUT = OUTDAT);

The odds ratio and condence interval are to be obtained from \_OUTDAT\_RATIOCI.

## 18.2.2 Analysis of binary (and categorical) data

### 18.2.2.1 Summary statistics for binary and categorical data

Summary statistics for discrete variables will be presented in contingency tables and will include count and frequency in each category. If applicable, confidence intervals will be derived as well based on the score method including continuity correction [Newcombe (1998)]:

With  $z$  as (1-alpha/2)-quantile of the standard normal distribution (SAS:  $z=PROBIT(1-alpha/2)$ ),  $n$  as total number of subjects (i.e. number of subjects in the denominator), and  $p$  as estimated crude incidence (number of subjects with event /  $n$ ) it is  $q = 1 - p$

Then the lower limit is

$$L = 100 \times \max \left( 0, \frac{2np + z^2 - 1 - z \sqrt{z^2 - 2 - \frac{1}{n} + 4p(nq + 1)}}{2(n + z^2)} \right)$$

and the upper limit is

$$U = 100 \times \min \left( 1, \frac{2np + z^2 + 1 + z \sqrt{z^2 + 2 - \frac{1}{n} + 4p(nq - 1)}}{2(n + z^2)} \right)$$

For binary response variables (e.g. for ACR20/50/70, HAQ-DI responder, PASI 75, IGA response) the placebo-adjusted response rates including 95% confidence interval will be derived.

SAS code for risk difference:

```
Proc freq data=acr order=formatted;
```

```
Tables response*trt/ riskdiff;
```

```
Run;
```

(Note the response value should be sorted with '1' ahead of '0'.)

Fisher's exact test will be applied to rare events (e.g., MCR), pairwise treatment group comparisons to placebo or active controls.

SAS code for Fisher's exact test:

```
Proc freq data=mcr order=formmatted;
```

```
Tables response*trt/Fisher;
```

```
Run;
```

Figures will be provided for primary and secondary variables, with means and 95% confidence intervals displayed across time for all the treatment groups.

### **18.2.2.2 Logistic regression**

Certain binary outcome variables, e.g. response outcomes, will be evaluated using a logistic regression model with treatment regimen, weight, stratum if applicable. Odds ratios will be computed for comparisons of AIN457 regimens versus control(s) utilizing the logistic regression model fitted.

SAS code for logistic regression:

```
Proc logistic data=aaa;
```

```
Class TRT STRATA / param=glm;
```

```
Model AVAL = TRT WEIGHT STRATA;
```

```
Lsmeans TRT / diff cl exp;
```

```
Ods output diffs=ls_m_diff;
```

```
Run;
```

In cases where separation is a concern, e.g. 0% response in one treatment (sub)group, an exact logistic regression model will be applied. To ensure convergence, this model will not include any continuous covariates.

```
Proc logistic data=aaa exactonly;
```

```
Class TRT STRATA / param=glm;
```

```
Model AVAL = TRT STRATA;
```

```
Exact TRT / estimate=both;  
Ods output exactoddsratio=exactoddsratio;  
Run;
```

### 18.2.3 Multiple Imputation

A multiple imputation will be performed based on MAR by treatment group for baseline weight, baseline and post-baseline of each parameter for visits up to the primary time point (Week 24) using Markov Chain Monte Carlo (MCMC) method with EM algorithm.

Impute the missing values 100 times (NIMPUTE) with a seed=457<studycode> as shown below:

```
proc mi data=min max=out=imp minmaxiter=10000000 nimpute=100 seed=4572306;  
    by trt;  
    var weight_base strata var1_base var1_week1-var1_week24;  
    mcmc chain=multiple initial=em;  
run;
```

If needed repeat for each component necessary to calculate the final score, e.g. as follows:

```
proc mi data=imp min=<min of scale> max=<max of scale> out=imp2 minmaxiter=10000000  
nimpute=100 seed=4572306;  
    by trt _imputation_ ;  
    var weight_base strata var2_base var2_week1-var2_week24;  
    mcmc chain=multiple initial=em;  
run;
```

The score and ACR response can now be calculated based on the complete data. The response rate will be calculated for each imputation and then combined using Rubin's rules.

In order to calculate the response rate for each imputation, PROC FREQ will be used as follows.

Calculate binomial proportion and standard error for each imputation.

```
proc freq data=<ACR20>;  
    by treat visit _imputation_ ;  
    tables <response> / binomial (level=2 cl=wilson correct) ;  
    ods output BinomialProp=imp_bpr;  
run;
```

Transpose the dataset for subsequent use with PROC MIANALYZE.

```
proc transpose data=imp_bpr out=imp_trs(drop=_name_);
```

```
by treat visit _imputation_ ;  
var nvalue1; id name1; idlabel label1;  
run;
```

Apply LOGIT transformation:  $y = \log(p/(1-p))$  and std. err. transformation:  $\langle \text{new se} \rangle = \text{se}/(p*(1-p))$

```
data logit;  
set imp_trs(rename=( _bin_ =p e_bin=se));  
by treat visit _imputation_ ;  
lmean=log(p/(1-p));  
lse=se/(p*(1-p));  
run;
```

The transformed binomial proportion estimates and standard errors are combined by applying Rubin's rules for multiple imputed data sets.

```
proc mianalyze data=logit;  
by treat visit ;  
modeleffects lmean;  
stderr lse;  
ods output ParameterEstimates=logitres;  
run;
```

The combined data should be transformed back using the following formula:  $p = 1/(1 + \exp(-y))$

```
data miexpres;  
set logitres;  
by treat visit ;  
resti = 1/(1+exp(-estimate));  
rlow = 1/(1+exp(-lclmean));  
rupp = 1/(1+exp(-uclmean));  
run;
```

Of note, sometimes all responses may be imputed to 0 or 1 at a given combination of response variable, treatment group and visit. Such cases should be considered separately. The combined final response rate would be the same as the original response but the 95% CI will be undefined.

The odds ratio will be derived using GENMOD for each imputation, then combined using Rubin's rules again.

```
proc genmod data = acr20_mi descending;
```

```

by avisitn _imputation_;
class trt_ TNFRESN ;
model aval = trt_ TNFRESN weight / link=logit dist=bin;
lsmeans trt_ / diff;
estimate 'AIN457 75mg mg vs Placebo' trt_ 1 0 -1;
estimate 'AIN457 150mg mg vs Placebo' trt_ 0 1 -1;
ods output Estimates=imp_est;

run;

proc mianalyze data=imp_est;
    by avisitn trt_ ;
    modeleffects LBetaEstimate;
    stderr StdErr;
    ods output ParameterEstimates=_res;

run;

```

## 18.2.4 Crude incidence and related risk estimates

### 18.2.4.1 Crude incidence and 100\*(1- $\alpha$ )% confidence interval

For  $n$  subjects, each at risk to experience a certain event with probability  $\pi$ , the crude incidence is estimated as  $p=x/n$ , where  $x$  is the number of subjects with the event.

Absolute and relative frequencies will be displayed as well as 95% confidence interval for the relative frequency based on the score method including continuity correction (Newcombe 1998).

With  $z$  as  $(1-\alpha/2)$ -quantile of the standard normal distribution (SAS:  $z=PROBIT(1-\alpha/2)$ ),  $n$  as total number of subjects (i.e. number of subjects in the denominator), and  $p$  as estimated crude incidence (number of subjects with event /  $n$ ) it is  $q = 1 - p$ .

Then the lower limit is

$$L = \max \left( 0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - \frac{1}{n} + 4p(nq + 1)}}{2(n + z^2)} \right)$$

and the upper limit is

$$U = \min \left( 1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - \frac{1}{n} + 4p(nq - 1)}}{2(n + z^2)} \right).$$



Note: if  $p = 0$  then  $L = 0$  and if  $p = 1$  then  $U = 1$ .

If appropriate, an exact  $100*(1-\alpha)\%$  confidence interval (Clopper-Pearson 1934) will be obtained by using the SAS procedure PROC FREQ with the EXACT BINOMIAL statement. However, the confidence interval derived via the score method including continuity correction will be the default in safety analyses.

#### **18.2.4.2 Odds ratio and $100*(1-\alpha)\%$ confidence interval**

For an investigational drug group with  $n_1$  subjects at risk, independent from the control group (e.g. placebo or comparator) with  $n_0$  subjects at risk, of whom  $x_1$  and  $x_0$  experience a certain event with probability  $\pi_1$  and  $\pi_0$  respectively, the odds ratio is estimated as

$\frac{p_1/(1-p_1)}{p_0/(1-p_0)}$  with  $p_1 = x_1/n_1$  and  $p_0 = x_0/n_0$ . A conditional exact  $100*(1-\alpha)\%$  confidence interval will be obtained by using the SAS procedure PROC FREQ with statement EXACT OR.

#### **18.2.4.3 Risk difference and $100*(1-\alpha)\%$ confidence interval**

For an investigational drug group with  $n_1$  subjects at risk, independent from the control group (e.g. placebo or comparator) with  $n_0$  subjects at risk, of whom  $x_1$  and  $x_0$  experience a certain event, the risk difference is estimated as  $p_1 - p_0$  with  $p_1 = x_1/n_1$  and  $p_0 = x_0/n_0$ .

Exact unconditional confidence limits for the risk difference will be obtained with SAS procedure PROC FREQ and option RISKDIFF in the TABLES statement, specifying the RISKDIFF option also in the EXACT statement.

### **18.2.5 Exposure adjusted incidence rate and related risk estimates**

#### **18.2.5.1 Exposure adjusted incidence rate and $100*(1-\alpha)\%$ confidence interval**

It will be assumed that for each of  $n$  subjects in a clinical trial the time  $t_j$  ( $j=1, \dots, n$ ) to the first occurrence of a certain event is observed, or if the event was not experienced, the (censored) time to the end of the observation period. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity  $\theta$ . The rate

parameter  $\theta$  will be estimated as  $\lambda = D/T$ , where  $T = \sum_{j=1}^n t_j$  and  $D$  is the number of subjects

with at least one event. Conditionally on  $T$ , an exact  $100*(1-\alpha)\%$  confidence interval for a Poisson variable with parameter  $\theta T$  and observed value  $D$  can be obtained based on (Garwood, 1936), from which an exact  $100*(1-\alpha)\%$  confidence interval for  $D/T$  will be derived as follows (Sahai, 1993; Ulm, 1990):

Lower confidence limit  $L = \frac{0.5c_{\alpha/2, 2D}}{T}$  for  $D > 0$ , 0 otherwise,

Upper confidence limit  $U = \frac{0.5c_{1-\alpha/2, 2D+2}}{T}$

where  $c_{\alpha,k}$  is the  $\alpha$ th quantile of the Chi-square distribution with k degrees of freedom.

The example below shows how this should be handled for cases where subjects switch treatment. In particular for summarizing ‘Any AIN’ as a group, one should take into consideration the sequence of treatments while calculating exposure time for subjects.

**Table 18-3 Examples for calculating exposure time for incidence rates (IR)**

1st treatment	1st exposure	2nd treatment	2nd exposure	Event days (in terms of study day)	Exposure for IR
Placebo	100 days	150 mg	200 days	50 (1st trt) 110 (10 days into 2nd trt)	Placebo: 50 days (event) 150 mg: 10 days (event) Any AIN: 10 days (event)

## 19 References

[SOP-5003921] Developing and Maintaining the Report and Analysis Plan

[FRM-5001452] Business Guidance for Conduct and Timing of RAP Discussions/ Meetings for Full Development Clinical Franchise and Oncology Studies

[FRM-5001451] Business Guidance for Responsibilities for RAP Development in Full Development Clinical Franchise and Oncology Studies

[FRM-5001454] Business Guidance for How to Approve the RAP Documentation in CREDI

[FRM-5001455] Business Guidance for Updating and Amending the RAP Documentation

[FRM-5001453] Business Guidance for M&S and IS&HE Involvement on the RAP Process

[SOP-0015116] Developing and Completing the Clinical Study Report

[SOP-0018880] Defining, Processing, and Reporting Protocol Deviations

AIN457A efficacy MAP M3, available in Cabinets//CREDI Projects/A/AIN457A /Administrative files/CIS (Clinical Information Sciences)/Biostatistics

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Alberti KGMM, Eckel RH, Grundy SM, et al (2009) Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; american heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. *Circulation*; 120: 1640-1645.

Biostatistical Guidance on Analysis Sets in Clinical Trials, available in Cabinets/CREDI TABULU/B&SR/CIS Process Documentation/Guidances (outside of ESOPS)/Others

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